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A Journal of Neurology

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MARCH, 1955

BRAIN

VOL. 78, PART I.

BENIGN FORMS OF INTRACRANIAL HYPERTENSION—"TOXIC" AND "OTITIC" HYDROCEPHALUS

BY

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I. A REVIEW OF THE LITERATURE

THE existence of a condition in which increased intracranial pressure occurs in the absence of a space-occupying lesion or of internal hydrocephalus was first recognized by Quincke (1893, 1897). It is sufficient for the time being to describe the syndrome as one of prolonged intracranial hypertension without ventricular abnormalities, focal neurological signs or disturbance of awareness or intellect, the most frequent symptoms being headache of moderate degree, obscurations of vision, diplopia and sometimes tinnitus; marked papillœdema and abducens palsies are the only signs. The cerebrospinal fluid is normal in composition, and the prognosis is almost invariably good, the condition subsiding in a few weeks or months. Cases with these features fall into two main groups, "otitic hydrocephalus," in which thrombosis of one or more dural sinuses following ear disease is held responsible, and "toxic hydrocephalus," in which as often as not there is no history of antecedent infection, and no cause of the raised pressure has been discovered. The terminology of the latter group has been confused; the condition has been described as Serous Meningitis (Quincke, 1897; Warrington, 1914; Sheldon, 1933), Toxic Hydrocephalus (McAlpine, 1937, 1952), Hypertensive Meningeal Hydrops (Davidoff and Dyke, 1937), Intracranial Pressure without Brain Tumour (Dandy, 1937) or of Unknown Cause (Sahs and Hyndman, 1939), Pseudotumour and Tumour Equivalent (Warrington, 1914; Bailey, 1920; Pseudoabscess (Adson, 1924), and more simply as Papillœdema of Indeterminate Ætiology (Yaskin *et al.*, 1949). To each of these terms there are objections; there is no meningeal reaction, no toxin has been clearly incriminated, and the term hydrops should not be applied to the leptomeninges; least appropriate of all is the term hydro-

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cephalus when applied to this condition, for there is no excess of fluid within the skull, the ventricular system being normal in size.

Because of the emphasis which has been placed upon thrombophlebitis of the dural sinuses, and especially of the sagittal sinus, as the only plausible explanation of the intracranial hypertension in such cases, the summarized findings from 46 examples of the otitic syndrome collected from the literature will be compared with those of 60 cases of the syndrome occurring in the absence of ear disease. In a later paper an analysis will be made of 95 cases of bilateral papillœdema without brain tumour or obstructive hydrocephalus, all but 7 of which have passed through the Neurosurgical Unit of St. George's Hospital in the past fourteen years.

It is plain that before the advent of ventriculography accurate diagnosis was virtually impossible. Cases reported before 1918 are therefore suspect, and indeed it was not until the appearance of the papers of Davidoff and Dyke (1937) and Dandy (1937) that a precise syndrome based on the *cardinal radiological feature, a normal ventricular system under increased pressure,* emerged clearly. The significance of a normal ventricular system under high pressure is best appreciated by considering the Monro-Kellie hypothesis in diagrammatic form (fig. 1). Fig. 1A is a crude representation of the incompressible brain tissue (shaded) through which runs the compressible vascular system. It is surrounded by the subarachnoid fluid (dotted), which communicates with the ventricle. These three components are enclosed in a rigid box open to the atmosphere only through the vascular system. Cerebrospinal fluid is formed by a process of secretion and filtration, and though in general its rate of formation varies inversely with the intraventricular pressure (Flexner, 1933) formation can continue in the face of considerable pressure. In the absence of disturbances of osmotic pressure, however, its rate of absorption depends directly upon the intracranial pressure (Mortensen and Weed, 1934). When the ventricle is obstructed (fig. 1B) its dilatation takes place at the expense of two components, the cerebral vascular bed and the film of fluid over the convexity of the hemispheres. Now if the cerebrospinal fluid pathways are obstructed outside the brain, even at the arachnoid villi themselves (as by mural thrombophlebitis of the sagittal sinus), or if formation outpaces absorption, only one of the three components can give way, namely the cerebral vascular bed (fig. 1c). As the ventricles and subarachnoid space are in communication and under equal pressure, the volume of both will increase at the expense of the volume of the vascular bed. It follows that there cannot be an external hypertensive hydrocephalus without some dilatation of the ventricles. It may well be, of course, that a large volume of extra fluid can be accommodated by a very

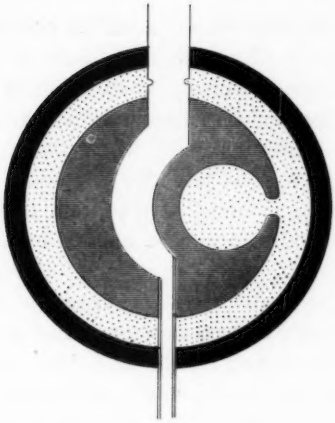

FIG. 1A.

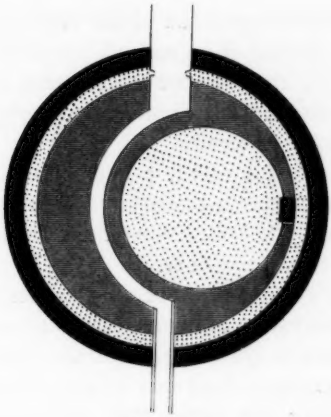

FIG. 1B.

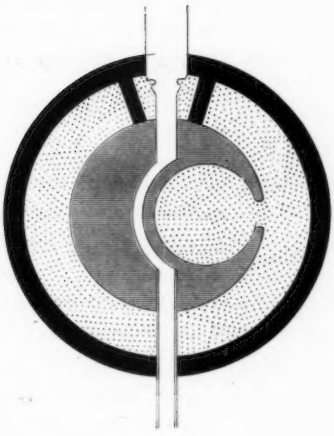

FIG. 1C.

FIG. 1D.

FIG. 1.—(A), Schematic representation of the three components of the intracranial system, the incompressible brain tissue (shaded), the vascular system open to atmosphere, and the C.S.F. (dotted); (B) during ventricular obstruction; (C) when there is obstruction at or near the points of outlet of the C.S.F.; (D) when there is obstruction of the venous outlet.

small increase in the depth of the subarachnoid space and that therefore no gross change in the size of the ventricles will be evident, but statistical examination should demonstrate that under these circumstances the ventricles are larger than normal. Not until the venous outlet is obstructed does a new factor make its entrance (fig. 1D). There can now

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be no compression of the vascular bed, and the ventricles will be normal or smaller than normal. Such a scheme is, of course, too simple to be really true because it represents the changes as being isotonic. But as a general rule, an undistorted ventricular system of normal size under increased pressure will occur in three conditions: (1) when there is obstruction of the venous outflow; (2) when there is active dilatation of the cerebral vessels; and (3) when there is swelling of the brain tissue itself. It is clear that the term hydrocephalus cannot be applied to any of these conditions.

The term "hypertensive meningeal hydrops" owes its origin to the observation of many authors of an abundance of fluid in the subarachnoid space at craniotomy. Dandy (1937) and Sahs and Hyndman (1939), however, recognized that an increase in the subarachnoid fluid could not exist within the intact skull without some increase in the volume of the ventricles. The deep subarachnoid space seen at craniotomy or through a burrhole is an artefact due merely to opening the skull and dura, when fluid from the ventricles, even if they are small, is displaced into that part of the subarachnoid space which has been opened to atmospheric pressure.

Otitic Hydrocephalus

As has already been pointed out, the finding of a ventricular system of normal size is a point—though admittedly a theoretical one—arguing against mural thrombophlebitis (as opposed to thrombosis of the lumen) of the superior longitudinal sinus being the cause of the raised pressure in cases following otitis; furthermore, suggestions that the thrombus might be confined to the lacunæ laterales are vitiated by O'Connell's (1934) demonstration that the lacunæ are empty of blood, a deduction from autopsy material amply confirmed by angiography: for although the sinus can be well seen the lacunæ are never visualized. Ventriculograms were carried out in only 18 of the 46 otitic cases summarized; in 16 the ventricles were normal or smaller than normal. Examination of the data from these cases (Table I), while it does not disprove the hypothesis that thrombosis of the superior longitudinal sinus is responsible for the increased pressure, indicates that thrombosis of the lateral sinus, and probably of the major lateral sinus, is the important factor. Thus in the 44 cases with observed otitis the disease affected the right ear in 25; 21 of these were submitted to mastoidectomy. Lateral sinus thrombosis was proven in 14 while granulations on the sinus wall or a perisinous abscess were found in a further 6; so in 20 out of the 25 right-sided cases the lateral sinus was definitely implicated by disease. 9 of the 13 cases with left-sided otitis were

TABLE I.—FINDINGS IN 46 CASES OF "OTITIC HYDROCEPHALUS" COLLECTED FROM THE LITERATURE*

A. *Age*

Age	*Number of cases*	*Age*	*Number of cases*
0–5	5	26–30	3
6–10	15	31–35	0
11–15	7	36–40	3
16–20	6	41–45	1
21–25	4	46–	0
		Not stated	2

B. *Sex*

Male	19
Female	24
Not stated	3

C. *Ventriculography*

Ventricles of normal size	13
Ventricles smaller than normal	3
Ventricles larger than normal	2

D. *Side of otitis*

	Right	*Left*	*Bilateral*	*Not stated*	*Total*
Frank otitis ...	25	13	5	1	44
Doubtful otitis ...	–	–	–	2	2

E. *Evidence of lateral sinus thrombosis*

	Right	*Left*
Mastoidectomy performed	21	9
Lateral sinus thrombosis seen	14	3
Granulations or perisinous abscess	6	2
Rigors or septicæmia	7	3
Sinus packed or jugular vein tied	11	4
Meningitis (including meningitis occurring later than the original purely hypertensive episode)	8	2

*Cases reported by: Leidler (1928); Cairns (1930); Symonds (1931. 1932, 1937, 1952); Carmack (1933); Garland and Seed (1933); Smith (1934); Rabbiner (1935); Fraenkner (1937); Bradbeer and Gibson (1937); Davidoff and Dyke (1937); McConnell (1937); Williams (1937); Gardner (1939); Ersner and Myers (1934); Ford (1944); Horowitz (1949); Smith and Mirmelstein (1949).

subjected to mastoidectomy; the lateral sinus was found thrombosed in only 3, but in a further 2 cases there were granulations on its wall, so the lateral sinus was seen to be diseased in 5 of the 9 cases. 4 of the 5 cases with bilateral otitis were subjected to mastoidectomy; in 2 the left lateral sinus was found thrombosed, while in 2 the sinuses were normal; we do not know, of course, which were the major sinuses in these cases.

The frequency with which a sixth cranial nerve palsy occurs on the side of the diseased ear in this condition has been regarded as circumstantial evidence of lateral sinus thrombosis, it being assumed that the

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nerve is involved by swelling as it lies in close proximity to the inferior petrosal sinus. In the 14 cases with squint this was homolateral in 9, contralateral in 2, and bilateral in 3; in no case was there a full Gradenigo's syndrome to suggest apical petrositis (Table II).

TABLE II

F. *Frequency of symptoms and signs*

Headache	36 cases	Papilloedema	41 cases
Vomiting	14 „	Squint	14 „
Diplopia	14 „	Nystagmus	6 „
Vertigo	4 „	Facial weakness	
Tinnitus	4 „	Peripheral	1 case
Drowsiness	4 „	Central, ipsilateral	2 cases
		Central, contralateral	1 case
		Pyramidal signs	4 cases
		Cerebellar signs	5 „

G. *Squint in relation to side of otitis*

Ipsilateral	
Right otitis, right abducens palsy	5
Left otitis, left abducens palsy	3
Bilateral otitis, bilateral abducens palsy	1—9
Contralateral	
Left otitis, right abducens palsy	1
Right otitis, left abducens palsy	1—2
Bilateral	
Right otitis, bilateral abducens palsy	1
Left otitis, bilateral abducens palsy	1
? otitis, bilateral abducens palsy	1—3

H. *Cerebrospinal fluid*

Records of cerebrospinal fluid available in	37 cases
Cells more than 5 per c.mm.	3 „
Protein more than 30 mg. per 100 ml.	2 „

It has always been a matter of surprise that a condition should be attributed to thrombosis of the sagittal sinus, mural or otherwise, and yet be free of clinical evidence of extension of the clot into cortical veins. Indeed, in the cases summarized, pyramidal or other focal cortical signs have been rare: a facial palsy of upper motor neurone type occurred only thrice, and other evidence of pyramidal involvement was found in only 4 cases; in no case were the signs severe, and no patient had a visual field defect. In only 2 of the cases summarized, those of Gardner (1939) and Fraenckner (1937) was angiographic visualization of the sinus attempted: in the former all the contrast medium introduced into the sagittal sinus had vanished by the time the exposure was made, while in the latter the posterior half of the sinus was probably occluded, but the angiogram was

not reproduced. More recently Ray and Dunbar (1951) and Ray, Dunbar and Dotter (1951) have employed the technique of direct venography of the superior longitudinal sinus originally used by Frenckner, demonstrating thrombosis of the lateral sinus in 2 cases of otitic hydrocephalus.

6 of the cases summarized were fatal, those of Carmack (1933, Case 2), Davidoff and Dyke (1937, Case 9), Gardner (1939, Cases 1 and 2), Ford (1944) and Symonds (1952). In Carmack's case no sinus thrombosis was found at autopsy; in Davidoff and Dyke's case the brain was normal, but no specific mention was made of the dural sinuses. In the 2 cases of Gardner and in Ford's case the salient features were old organized thrombus in one lateral sinus, considered to be responsible for the original episode of pure intracranial hypertension, and recent suppurative thrombophlebitis of the superior longitudinal sinus accompanying a terminal acute purulent meningitis, the terminal illness being clearly distinguishable both in time and nature from the earlier hypertensive episode in all 3 cases. In Symonds' case, in which death followed lumbar puncture, there was thrombosis of the lateral sinus to the torcular.

It thus appears that the only common finding at operation or at autopsy is thrombosis of a lateral sinus; and further, indirect, evidence against the theory that sagittal sinus thrombosis must play a part is to be found in the experimental work of Beck and Russell (1946), who demonstrated that the superior longitudinal sinus is extraordinarily resistant to agents which provoke thrombosis with ease in the systemic veins. Lateral sinus thrombosis alone, however, is not enough to account for the syndrome. Lateral sinus thrombosis is relatively common, while otitic hydrocephalus is rare; although both Dill and Crowe (1934) and Ford (1944) found that raised intracranial pressure occurred in half their cases of lateral sinus thrombosis, the intracranial hypertension in such cases is neither so great nor so prolonged as it is in the hypertensive syndrome under discussion. For the production of this condition the thrombus must presumably affect the major sinus or extend to the torcular, and in addition there must probably be cerebral œdema, widespread in view of the symmetry of the ventricles, and of a type not associated with impairment of consciousness; for while many authors have commented on the fact that the intracranial hypertension may subside in a few days after lumbar puncture (a fact scarcely consistent with venous obstruction as the sole cause of the pressure) it is of interest that the intracranial hypertension may persist for months even though the otitis lasted only a few days; the work of Beck and Russell (1946) suggests that canalization of a thrombus would occur in a few weeks.

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Toxic Hydrocephalus

Instances of prolonged intracranial hypertension with a normal ventricular system occur more commonly without than with a history of otitis or disease of the nasal sinuses. Their similarity to cases of otitic hydrocephalus is merely a reflection of the fact that in both conditions the symptoms are solely those of raised intracranial pressure; there is one small difference—squint is slightly more common in the otitic cases. Only 3 of Quincke's cases are acceptable by modern standards, and in none of these was the illness preceded by an infection. The general features of the syndrome will be described with reference to the findings in 60 acceptable cases collected from the literature.

The principal incidence is in females at the age of puberty and in the early twenties (Table III). The absence of cases before the age of 5 or

Table III.—Age and Sex in 60 Cases of Benign Intracranial Hypertension Without Otitis Collected From The Literature *

Age	*Male*	*Female*	*Total*
0–5	0	0	0
6–10	1	4	5
11–15	3	7	10
16–20	1	6	7
21–25	3	11	14
26–30	1	4	5
31–35	1	5	6
36–40	3	2	5
41–45	3	3	6
46–50	1	1	2
51+	0	0	0
	17	43	60

* Cases reported by: Quincke, Cases 2, 8, 9 (1897); Warrington, Cases 1, 2, 3 (1914); Sheldon (1933); McAlpine, Cases 1 to 5 (1937); Davidoff and Dyke, Cases 1 to 4, 8, and 10 to 15 (1937); Dandy, Cases 1 to 22 (1937); Sahs and Hyndman, Cases 1 to 5 (1939); Phillips, Cases 1 to 5 (1948); Yaskin *et al.*, Cases 2, 3, 8 to 10, and 12 (1949).

after the age of 50 is unexplained but is shown also in the personal series to be reported later. The ætiological agents which have been held responsible in these non-otitic cases have been so numerous and diverse that one must suspect that none is in fact a direct cause. Quincke cited alcoholism, head injuries, overwork, menstruation, pregnancy and exposure to cold; Warrington added pelvic disease and tuberculosis, while Sheldon (1933) and McAlpine (1937, 1952) suggested an allergic basis for their cases. In fact the condition occurs more frequently without (33

cases) than with a history of an antecedent infection (27 cases). It will be seen from Table IV that cachexia and those chronic diseases commonly held responsible for primary cerebral venous thrombosis are conspicuous by their absence.

TABLE IV.—NATURE OF PRECEDING ILLNESS

A.	None	33
B.	Sore throat	4
	Brief febrile illness	4
	Coryza	3
	Head injuries	2
	Pelvic disorders (operation 2; delivery, 1; menorrhagia, 2) ...	5
	Cholecystitis	2
	Previous crural thrombosis	2
	Remote otitis	1
	Juvenile hip disease	1
	Pleural effusion	1
	Hydrarthrosis	1
	Anæmia	1

Headache was by far the commonest of early symptoms, being present in 47 cases; vomiting was associated with it in only 10, and neck stiffness occurred early in 5. The early headaches were associated with photophobia in 3, blurred vision in 4, and progressive visual failure in 6 cases. 3 patients had dysæsthesiæ of one limb or of one side: dysæsthesiæ were generally late symptoms, and they occurred only in cases with very high intracranial pressure. Only 1 patient had convulsions. 24 patients had diplopia sooner or later in the illness; no less than 10 of Davidoff and Dyke's 15 patients had failing vision by the time they were admitted. In 2 cases in the series the onset was associated with a swollen face; both were women aged 34, one had a pleural effusion and one had a history of cholecystitis, and in neither did symptoms nor signs of cavernous or cortical venous thrombosis later appear. 5 patients were drowsy, and 2 pyrexial, at the onset; 8 patients became drowsy at some stage of the illness.

There was apparently little about the general appearance of these patients to give a clue to the ætiology. While 3 were undernourished, no less than 14 were conspicuously obese. 4 had low fever on admission, 2 had leucocytosis; albuminuria without hypertension was present in 3, glycosuria in 1. 2 patients were anæmic, and 2 had a positive Wassermann reaction in the blood but no evidence of active syphilis. 1 patient had a streptococcal pelvic abscess and polyarthritis and had previously had a scarlatiniform rash, and 1 had early lymphadenoma with no evidence of involvement of the nervous system, or of obstruction of the superior vena cava.

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57 of the patients had papillœdema (the 3 without it being Quincke's) and the swelling was of 4D or over in 16; retinal hæmorrhages were noted in 19. The papillœdema was invariably bilateral and was conspicuously unequal in only 3 instances. 4 patients showed some degree of optic atrophy by the time of admission. The visual acuity was recorded in 48 cases and in 21 of these it was diminished, the impairment affecting 1 eye only in 8; such unilateral visual failure could not be correlated with a higher degree of discœdema in the failing eye than in the eye with normal vision. The degree of visual failure in the 21 cases bore no definite relationship to the amount of disc swelling or to the duration of symptoms; in 17 cases the visual fields showed constriction, with enlargement of the blind spots. Squint was present in 12 cases, due to unilateral or bilateral external rectus palsies; 1 patient had in addition an internal rectus palsy. The pupils showed no special features. Nystagmus was present in 7 cases. Involvement of other cranial nerves was not encountered. Facial weakness of upper motor neurone type was present in 5 cases and mild pyramidal signs were detected in the limbs in 5; 1 patient developed a transient spastic quadriparesis.

Ventriculography was performed on 45 of the 60 cases collected from the literature. In no case was there distortion or displacement of the ventricular system. The ventricles were reported as being normal in 29 cases, small in 14, and slightly dilated in 2. In 11 cases with small ventricles in which the lumbar pressure was recorded the average pressure was 372 mm. fluid, whereas in 16 cases in which the ventricles were of normal size the average lumbar pressure was 347 mm. It would thus appear that the cases with the highest pressure were those in which the cranial cavity contained the smallest amount of cerebrospinal fluid (as judged by the ventricular size, which, in the absence of obstruction, bears a direct relationship to the total cerebrospinal fluid volume); for this reason the term hydrocephalus is not applicable to the condition. In only 5 instances was the amount of cerebrospinal fluid removed at lumbar puncture recorded, the volumes being 15, 15, 26, 30, and 75 ml.; the last figure represents the result of total drainage of the fluid during lumbar encephalography.

Angiography was not employed in any of the cases summarized. Radiological evidence of thrombosis of the superior longitudinal sinus in 2 somewhat similar cases has recently been provided by Ray and Dunbar (1951) and Ray, Dunbar and Dotter (1951). One of these, however, Case 1 (1951) displayed features, notably "minor convulsive seizures" and an episode of confusion lasting several days, which are rare in the syndrome outlined above, and moreover angiography later showed occlusion of the

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right internal carotid artery. In Case 2, a young man, an episode of intracranial hypertension preceded by seven months a deep thrombophlebitis of one leg; two years after his first illness a direct sinogram showed obstruction of the posterior third of the superior longitudinal sinus. Their third non-otitic case was a young man with unilateral convulsions due to cortical and sinus thrombosis; he had two episodes of crural thrombophlebitis, and in view of the convulsions is manifestly not an example of the syndrome in question.

15 of the patients had their symptoms for less than a month, and 11 for more than a year (maximum five years), the remainder being ill for between one and twelve months. 47 of the cases improved rapidly after subtemporal decompression or repeated lumbar punctures, but the authors did not always state the time interval after which complete recovery was noted. Only 1 patient had a relapse. Subtemporal decompression was performed in 29 cases, and in 4 of these the decompression was still tense between two and four years after the operation; in 2 patients it was noted that the tension of the decompression varied rapidly from hour to hour.

3 patients died (Warrington, 1914). The post-mortem findings cast no light on the pathology of the condition. One of Warrington's patients died of typhoid fever four years after the episode of intracranial hypertension, and the brain was normal. One died after seven months and had a slight meningeal reaction; the third case died after a few weeks and the only abnormality found was a funnel-shaped dilatation of the upper part of the fourth ventricle and lower part of the aqueduct; the third and lateral ventricles, and the foramina of Magendie and Luschka being normal. The state of the dural sinuses was not commented on specifically in any of these cases. The case reported by Bailey (1920) as an example of pseudotumour, but not included in those summarized in this paper, had a subacute hæmorrhagic meningoencephalitis which had caused drowsiness, ocolumotor palsies and increased intracranial pressure. The term pseudotumour should be reserved for cases in which ventriculography demonstrates a space-occupying lesion, biopsy gives equivocal results, and recovery ensues.

The question will be raised whether any other condition can be incriminated as the cause of the raised intracranial pressure in the cases summarized. Dandy's twenty-first case (1937) was probably an example of puerperal thrombophlebitis similar to those described by Martin (1941) except for the fact that although there were focal cortical symptoms there were no focal signs. In Sheldon's (1933) and McAlpine's (1937, 1952) cases there is strong evidence that a process of sensitization to bacterial toxins was in some way responsible; but while cerebral and meningeal symptoms,

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with increased intracranial pressure, are known to occur occasionally as allergic phenomena they are usually fairly closely related to an allergen and often accompanied by urticaria or angioneurotic œdema; urticaria was present in none of the cases summarized, and swelling of joints was present in only 2. 2 patients may have had a prolonged episode of intracranial hypertension after a subarachnoid hæmorrhage (Dandy, 1937, Cases 17 and 20). Such a condition may result from obstruction of the cerebrospinal fluid pathways by clot, in which case the obstruction should be demonstrable by air studies, from increase in the osmotic pressure of the cerebrospinal fluid, or occlusion of the arachnoid villi by blood pigments. There should then be an increase in the volume of the cerebrospinal fluid and a slight increase in the size of the ventricles, as was found by Bagley (1929) in animal experiments. In both Dandy's cases the ventricles were of normal size.

Summary

46 cases of "otitic hydrocephalus" have been collected from the literature. There is no satisfactory evidence that mural thrombophlebitis of the superior longitudinal sinus, with impairment of absorption of cerebrospinal fluid, is responsible for the raised pressure. Since the ventricles are of normal size the use of the term hydrocephalus is incorrect. Such radiological and pathological evidence as is available suggests that the cause is thrombosis of a lateral sinus which happens to be the major one. A process of cerebral œdema may, however, contribute to the raised intracranial pressure, for canalization of a thrombosed sinus occurs in a few weeks, whereas the intracranial hypertension in these cases may last for many months.

With regard to non-otitic cases, here called "benign intracranial hypertension," of which 60 cases have been collected from the literature, it appears that prolonged episodes of intracranial hypertension with a normal ventricular system occur more often without than with a history of a preceding infective process elsewhere in the body. The supposed ætiological agents are numerous and diverse. The condition is more than twice as common in women as in men, and it usually lasts two to six months. Vision tends to fail earlier in these cases than in cases of papillœdema due to cerebral tumour. The evidence that dural sinus thrombosis is responsible in this group of cases is scanty, and the absence of ventricular dilatation with external hypertensive hydrocephalus makes it improbable that overproduction of cerebrospinal fluid is the cause. The deep subarachnoid space often found at craniotomy is an artefact caused merely by opening the skull.

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II. An Analysis of 95 Cases of Papilloedema of Obscure Origin

The principal objectives in collecting together a large number of cases of intracranial hypertension of obscure ætiology were fourfold. Firstly, it seemed reasonable to expect that in a large series a number of ætiological and clinical entities might be recognizable. Secondly, if thrombosis of the superior longitudinal sinus were indeed the cause, as has often been suggested, then in a large series of cases clinical evidence of extension into cortical veins must surely be forthcoming, and cases intermediate between the purely hypertensive condition and the classical picture of sagittal sinus thrombosis would be recognized. Thirdly, it was felt that only by prolonged follow-up examination could the possibility of the later development of a brain tumour, notwithstanding the initial normal ventriculogram, be excluded. Fourthly, it has frequently been observed that visual failure seems to occur earlier in these cases than in people with cerebral tumours not involving the visual pathways, and an attempt has been made to elucidate the mechanism of this failure of vision, which is often clearly different from the peripheral constriction commonly associated with secondary optic atrophy. This last aspect will be dealt with in a separate communication.

With seven exceptions the cases summarized in this paper have passed through the Neurosurgical Unit of St. George's Hospital under the care of Mr. Wylie McKissock or Mr. Valentine Logue in the past fourteen years. A further 15 patients were discarded because they did not fulfil the criteria stated below; 2 of these, with bilateral papilloedema, no other neurological signs, and normal ventriculograms, later proved to have tumours, and the remainder suffered from mild chronic meningitis.

Initially, the criteria for inclusion in the series were as follows: (1) there must be bilateral discœdema; (2) there must be symptoms which, taken in conjunction with the ophthalmoscopic appearance, add to the probability of there being raised intracranial pressure; (3) there must be no definite evidence of a focal cerebral lesion, and neither must there be such obfuscation of the mind as to suggest a diffuse cerebral disease; (4) there must be no systemic hypertension, or any other general condition which could account for the papilloedema; and (5) ventriculography must have revealed no evidence of a cerebral tumour or of obstruction of the cerebrospinal fluid pathways. Early attempts to separate out a number of clinical groups failed for the reason that the symptoms and signs are merely those of raised intracranial pressure. The cases were therefore divided into those with and those without objective evidence of raised intracranial pressure (apart from disc swelling), in order to be sure

of handling a fairly pure sample. The composition of the groups was as follows:

GROUP A: Cases with bilateral disc swelling, symptoms of raised intracranial pressure, and objective evidence of raised pressure (raised lumbar pressure, radiological signs of pressure, or very high dural tension at ventriculography	60 cases
GROUP B: Cases with bilateral disc swelling, symptoms of raised intracranial pressure, but no objective proof of it	20 cases
GROUP C: Cases with bilateral disc swelling, indefinite symptoms, and no evidence of raised intracranial pressure	15 cases

Groups B and C, though they have been followed up, have been discarded, and only the 60 cases in Group A are analysed. Group C consisted of an interesting series of diagnostic pitfalls in which coincidental symptoms such as headache or blurring of vision had drawn attention to swelling of both discs; the group comprised the following:

Hyaline bodies in the optic nerves	5
Chronic progressive papilloretinitis of unknown type, later found to be associated with chronic uveitis	2
Recurrent or subacute iridocyclitis with chronic bilateral disc swelling	4
Bilateral chronic optic neuritis	1
Congenital vascular anomaly of the discs	1
"Pseudoneuritis"	2

Of the 60 cases forming Group A, 36 were personally examined when first admitted to hospital, and 26 of these were again seen at a follow-up clinic, the remainder being followed up by letter. A further 19 cases, who had been admitted to hospital before 1948, were seen only at the follow-up clinic, when a fresh history was taken; 5 patients have not been traced. The maximum period of follow-up of the personally examined cases has been six years, the minimum ten months; of the cases examined by me only at the follow-up clinics the maximum period that had elapsed since the illness was fourteen years and the minimum three years.

Group A has been further subdivided as follows:

(1) Otitic	11 cases
(2) Probable cerebral thrombophlebitis	2 cases
(3) Group A less (1) and (2) above,	
(*a*) with a history of antecedent infection or mild head injury	16 cases
(*b*) without such history	31 cases
	60

As an example of the non-otitic condition one case will be cited. The case-reports of the remainder have been given in full elsewhere (Foley, 953).

Case 89. St. George's Hospital No. 139939.—Admitted 19.10.50, discharged 10.12.50; readmitted 11.3.51, discharged 16.3.51.

P. K., female, aged 40, single; a postmistress.

Family history.—Nothing of note.

Previous illnesses.—In 1945 she had varicose veins with phlebitis, but she had had no recurrence since then.

Present illness.—Five months before admission she began to notice transient darkening of vision lasting two or three seconds and occurring most often on rising from a sitting position, or on turning the head. Often if somebody knocked at the door she would have to stand still after getting up because she was temporarily blind. She had always had mild frontal headaches at the onset of menstruation, but now she began to have more severe headaches, worse at the end of the day, but not affected by coughing or stooping; there was no vomiting. She had four attacks of double vision lasting two or three minutes.

Three months before admission, while in bed at night, she had two attacks consisting of a sudden flash of light in front of both eyes "as if somebody had turned the light on and off." One day she noticed that she could no longer smell flowers, and that she could no longer taste her food properly. Her headaches slowly increased in severity, but did not interfere with her sleep. She was troubled by a continuous hissing noise in the right ear, but there was no deafness or giddiness. The obscurations of vision became increasingly frequent, latterly occurring at least every half-hour, but if she lay quietly in bed she could avoid an obscuration for three or four hours. In the three months before admission she noticed a slight deterioration of vision in both eyes. Two months before admission she had a mild continuous tingling in the finger-tips of the right hand. Her periods, previously regular, now became scanty, lasting two or three days instead of five or seven as before.

Her memory remained normal, and speech was unaffected. There was no disturbance of consciousness nor alteration of sleep rhythm. At no time did she notice neck stiffness or swelling of the face or eyelids. Her general health remained good, and there was no change in her facial appearance or bodily habitus. Her weight was steady, her appetite good and her thirst normal.

On admission on 19.10.50 she was a well-nourished, plump afebrile woman with no abnormality on general examination except for a blood pressure of 170/110, falling to 140/90 during her stay in hospital. She was mentally clear, and speech was normal. There was bilateral hyposmia. Visual acuity was 6/9, 6/12 and the fields were full on perimetry. There was intense bilateral papillœdema, without hæmorrhages or exudates. The pupils and ocular movements were normal (nystagmus had been noted before admission). The tendon reflexes were brisk, those on the left side being slightly brisker than those on the right; otherwise there were no abnormal neurological signs.

The blood count, sedimentation rate, blood fibrinogen and blood urea were normal; the W.R. was negative. The urine contained no albumen, casts or red cells; the urea clearance and urinary dilution and concentration tests were normal.. X-rays of the skull showed evidence of raised pressure; the electroencephalogram was within normal limits. A right percutaneous arteriogram revealed no abnormality; the superior longitudinal sinus was clearly visualized and appeared to be normally filled. At ventriculography the dural tension was high; the ventricles were normal in size, shape and position. The ventricular fluid contained 400 red cells and 25 lymphocytes per c.mm., and normal quantities of protein, sugar and chloride. At lumbar punc-

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ture three days after the ventriculogram the initial pressure was 490 mm.; the pressure showed considerable variations, though the patient was not nervous; whenever she was addressed the pressure rose quickly above 600 mm. Compression of either right or left jugular vein caused a rise of pressure above 600 mm. After the removal of 20 ml. of faintly blood-stained fluid the pressure was 110 mm. The fluid contained 1,200 red cells and 21 white cells per c.mm.; protein, sugar and chlorides were normal.

After lumbar puncture headache was unchanged but she noticed a decline in visual acuity. The papillœdema remained intense, but without hæmorrhages or exudate. Three weeks after admission visual acuity was R. 6/6, L. 6/36; there was constriction of the fields and enlargement of the blind spots, and on the left side a small paracentral scotoma was detected. The lumbar pressure was now 300 mm. One month after admission visual acuity in the left eye had fallen 6/60, and a right subtemporal decompression was performed; the subarachnoid space was of normal depth. Almost two months after admission visual acuity was R. 6/9, L. 6/36, the papillœdema was slightly less marked, and both discs had a slightly grey tinge. Perimetry showed no further constriction of the fields, but the left paracentral scotoma had enlarged and broken out to the periphery. The subtemporal decompression was still tense, but she was discharged.

Three months later she was readmitted. She had had only occasional right temporal headaches on bending, probably due to the decompression. She was slightly obese; her blood pressure was 140/95. The decompression was bulging about ¾ in. above the surface but was pulsating. She still had hyposmia. Visual acuity was R. 6/6, L. 6/60; the right field was slightly constricted and the blind spot was enlarged; in the left field the paracentral scotoma had broken away from the temporal defect. Both discs were pale, with slightly blurred margins, except for the temporal margin of the left disc, which was sharply defined, as might be expected from the presence of the scotoma. At lumbar puncture the pressure was 270 mm., and the fluid was normal. Seven months later she was free of symptoms, though visual acuity in the left eye was still 6/36; the fundi and fields showed no change, but the decompression was still bulging. Since then she has remained well.

This case exhibits most of the typical features of the condition—the onset in a woman in the fourth or fifth decade, the absence of an antecedent infection, the very high intracranial pressure without evidence of local cerebral disease, the slight pleocytosis of the ventricular fluid, impairment of vision due not to secondary optic atrophy alone but to the development of a paracentral scotoma, the prolonged course (intracranial hypertension persisting a full seventeen months), and the good prognosis.

Analysis of Data From Group A

Evidence of Raised Pressure

In the 60 cases in Group A, all of whom had bilateral papillœdema, proof of intracranial hypertension was obtained by lumbar puncture (usually after ventriculography) in 43, the upper limit of normal being taken as 200 mm. fluid in the horizontal position. In none of these cases did manometric tests provide evidence of lateral sinus thrombosis; 17 of them had clinoid erosion on skull X-rays, and 12 had suture diastasis. In

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TABLE I.—MEAN VENTRICULAR DIAMETERS IN MM. OF THE VARIOUS AGE-GROUPS

	Controls	*No.*	*Av. age*	*Left*	*Right*	*Av. right and left*
Age-range 6–10	Males	9	7·1	20·778	21·333	21·056
	Females	5	5·9	19·000	18·400	18·700
	Av. male and female	14	6·6	20·143	20·286	20·213
	Group A					
	Males	4	6·5	21·500	19·500	20·500
	Females	4	8·0	21·250	20·250	20·750
	Av. male and female	8	7·2	21·375	19·875	20·625
Age-range 11–20	*Controls*					
	Males	8	15·4	22·625	20·875	21·750
	Females	6	15·0	23·167	23·167	23·167
	Av. male and female	14	15·3	22·857	21·857	22·350
	Group A					
	Males	3	12·7	21·312	22·311	21·833
	Females	6	13·8	20·667	20·333	20·500
	Av. male and female	9	13·4	20·889	21·000	20·944
Age-range 21–30	*Controls*					
	Males	18	25·7	22·056	22·167	22·112
	Females	12	26·8	22·250	21·083	21·667
	Av. male and female	30	26·1	22·133	21·733	21·933
	Group A					
	Males	1	26·0	22·000	26·000	24·000
	Females	6	23·2	23·333	23·516	23·417
	Av. male and female	7	23·6	23·143	23·857	23·500
Age-range 31–40	*Controls*					
	Males	6	36·3	22·500	21·500	22·000
	Females	15	34·1	21·467	21·200	21·333
	Av. male and female	21	34·3	21·762	21·286	21·524
	Group A					
	Males	4	35·5	23·000	23·250	23·125
	Females	9	36·6	21·111	21·333	21·222
	Av. male and female	13	36 308	21·692	21·923	21·808
Age-range 41–50	*Controls*					
	Males	9	43·7	22·222	21·667	21·944
	Females	10	44·5	22·300	22·000	22·150
	Av. male and female	19	44·1	22·264	21·844	22·053
	Group A					
	Males	—	—	—	—	—
	Females	6	45·8	21·833	19·833	20·833
	Av. male and female	6	45·8	21·833	19·833	20·833

the 17 cases not subjected to lumbar puncture high dural tension was noted, and 6 of these also had radiological evidence of increased pressure.

VENTRICULAR SIZE

Ventriculography was performed in 58 of the 60 cases, and all their ventriculograms were normal. Of the two without ventriculograms one was an example of the otitic syndrome, and the other was a classical example of the syndrome following upper respiratory tract infection,

TABLE II.—DIAMETER OF LATERAL VENTRICLES IN CASES OF GROUP A AND IN 113 "NORMAL" VENTRICULOGRAMS*

Controls	*Mean diameter, mm.*	*S.D.*	*Number of cases*
Left ventricle (all ages)	21·8	2·59	113
Left ventricle (age under 50)	21·9	2·55	100
Right ventricle (all ages)	21·25	2·61	113
Right ventricle (age under 50)	21·41	2·63	100
Averaged L and R (all ages)	21·53	2·40	113
Averaged L and R (age under 50)	21·645	2·41	100
Group A			
Left ventricle (all ages)	21·7	2·35	45
Left ventricle (age under 50)	21·7	2·38	44
Right ventricle (all ages)	21·42	2·67	45
Right ventricle (age under 50)	21·4	2·69	44
Averaged L and R (all ages)	21·6	2·31	45
Averaged L and R (age under 50)	21·5	2·33	44

	Left Ventricle in Relation to Right			
	Greater	*Equal*	*Less*	
Controls	57	26	36	113
Group A	20	12	13	45
	71	38	49	158

*It is of interest that in the control series the left ventricle is slightly larger than the right in a significant number of cases; this difference is not significant in the cases of Group A.

and was included in the series by kind permission of Dr. McAlpine; this case has been reported in full (McAlpine, 1952). The determination of the size of the ventricular system in such cases being of considerable importance for theoretical reasons, the ventricular diameter was measured in 46 cases of which the films were still available and filling was good enough to permit accurate measurement, and compared with that of 113 "normal" ventriculograms. The 113 control cases comprised persons suffering from migraine, psychoneurotic headaches, hysteria and epilepsy of mild degree without intellectual deterioration or neurological signs, collected over a period of fourteen years. The transverse diameters of the anterior horns of the lateral ventricles were measured to the nearest millimetre in standard anteroposterior projections made on a Lysholm-Schonander table (Tables I and II). In the control series the left ventricle was slightly larger than the right in a significant number of cases; this difference was not significant in the cases of Group A (unfortunately information about handed-

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ness was rarely available in the records of the control cases). The comparison indicated that the ventricular size in cases of benign intracranial hypertension is in fact within the limits of normal (fig. 1). The significance of a normal ventricular system under high pressure has

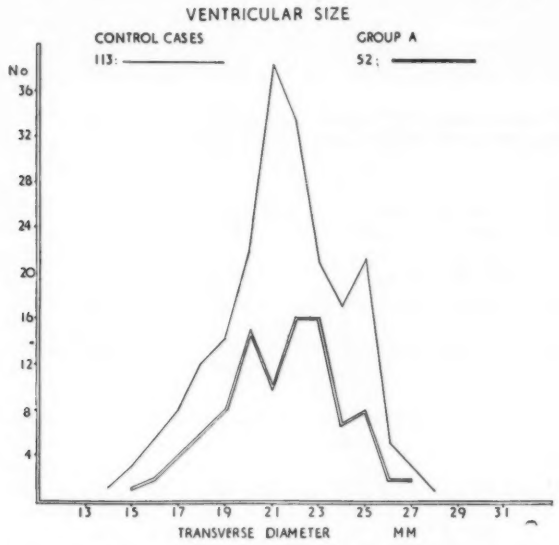

FIG. 1.—Ventricular diameter in cases of Group A and in 113 normal controls.

TABLE III.—VENTRICULAR DIAMETER IN RELATION TO LENGTH OF HISTORY BEFORE ADMISSION

Weeks	*Number of cases*	*Averaged right and left diameters, cm.*					
0–	—	—					
1–	3	1·7	2·3	2·4			
2–	6	1·9	2·15	2·25	2·3	2·45	2·9
3–	4	1·8	1·9	2·05	2·25		
4–	7	1·9	1·95	2·0	2·05		
		2·1	2·2	2·45			
5–	6	1·8	2·1	2·15	2·2	2·3	2·45
6–	6	1·75	2·0	2·0	2·1		
		2·3	2·3				
7–	1	2·05					
8–	5	1·75	2·25	2·25	2·35	2·45	
9–	—	—					
10–	1	2·1					
11–	—	—					
12–17	4	1·95	2·3	2·3	2·3		
18–24	5	2·0	2·25	2·3	2·6	2·6	
25–52	5	1·55	1·75	2·0	2·1	2·55	

already been discussed in the previous paper. The size of the ventricular system in cases of Group A does not appear to depend on the duration of the illness before admission; cases with a duration of up to four weeks had a mean ventricular size of 21·5 mm.; those with a duration of five to nine weeks had a mean ventricular size of 21·3 mm., while those with a duration of ten weeks to two years had a mean size of 21·7 mm., as shown in Table III. The size of the ventricular system does not appear to vary significantly with the pressure, but it is important to note that the measurements of lumbar pressure were made at an interval varying from 24 to 72 hours after ventriculography (Table IV).

TABLE IV.—RELATION BETWEEN SIZE OF VENTRICLE AND C.S.F. PRESSURE*

C.S.F. pressure mm. fluid	*Number of cases*	*Diameter, cm. (averaged R+L)*				
100–	—	—				
125–	—	—				
150–	2	2·4	2·25			
175–	2	2·3	1·7			
200–	2	2·45	2·3			
225–	3	2·3	2·25	2·1		
250–	2	1·55	1·8			
275–	2	2·2	1·75			
300–	6	2·6	1·95	2·05		
		1·9	1·75	2·15		
325–	2	2·3	2·1			
350–	5	2·0	2·1	2·3	2·0	2·15
375–	—	—				
400–	4	2·3	2·3	2·55	2·0	
425–	—	—				
450–	1	2·45				
475–	2	2·6	2·25			
500–	2	2·3	2·2			
525–	—	—				
550–	2	2·45	2·0			
575–	—	—				
600–	1	1·9				

*The mean ventricular diameter of the 19 cases with pressure under 300 mm. = 2·075; that of the 19 cases with pressure over 300 mm. = 2·22 cm. Standard deviation = 0·349. The standard error of the difference between the two means = 0·165, while the difference between the two means = 0·145; i.e. the difference in the two groups is not significant.

ABSENCE OF GENERAL CAUSES OF PAPILLŒDEMA

No extracerebral cause of papillœdema, such as malignant hypertension, polycythæmia vera or other blood dyscrasia, emphysema and chronic idiopathic hypoparathyroidism, was detected in any of the cases.

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9 cases had, or later developed, systemic hypertension, but in none was the hypertension severe enough to account for the raised intracranial pressure, and in none was there renal failure. The cases in Group A did not appear to be persons more prone to headaches than the general population. Of the 60 patients only 13 gave a history of headaches before the onset of the episode or raised intracranial pressure. In only 3 of these were the headaches of classically migrainous type, and 1 of these developed a homonymous quadrantic field defect during her illness. Quincke suggested that some of his cases of "serous meningitis" might be due to angioneurotic œdema of the meninges, but there is nothing in the present series to support this, though there is, as will be shown later, a vague relationship between menstrual disorders and benign intracranial hypertension; a long history of headaches was more common in the patients with menstrual disorders.

Age and Sex

Taking all the 60 cases together, females predominate (44 to 16). In the cases with otitis or probable cerebral thrombophlebitis, on the other hand, males and females are almost equally represented (Table V). It is

Table V.—Age and Sex in 60 Cases

	All cases		*Otitic and thrombophlebitic*		*Remainder*	
Age	*Male*	*Female*	*Male*	*Female*	*Male*	*Female*
0–	—	—	—	—	—	—
5–	4	5	2	3	2	2
10–	5	6	1	3	4	3
15–	1	5	0	1	1	4
20–	0	4	0	0	0	4
25–	2	3	2	0	0	3
30–	2	3	0	0	2	3
35–	2	8	0	1	2	7
40–	0	3	0	0	0	3
45–	0	5	0	0	0	5
50–	0	2	0	0	0	2
55–	0	0	—	—	—	—

reasonable to suppose that the 60 cases of Group A represent a number of conditions difficult to distinguish clinically because their symptoms and signs are merely those of raised intracranial pressure. However, the age incidence shows two main peaks, one in the second and the other in the fourth decade (fig. 2). There were 11 otitic cases, and these form an ætiologically homogeneous whole. As has already been mentioned, study of 46 otitic cases collected from the literature made it clear that the most constant pathological change in such cases is thrombosis of the lateral sinus which

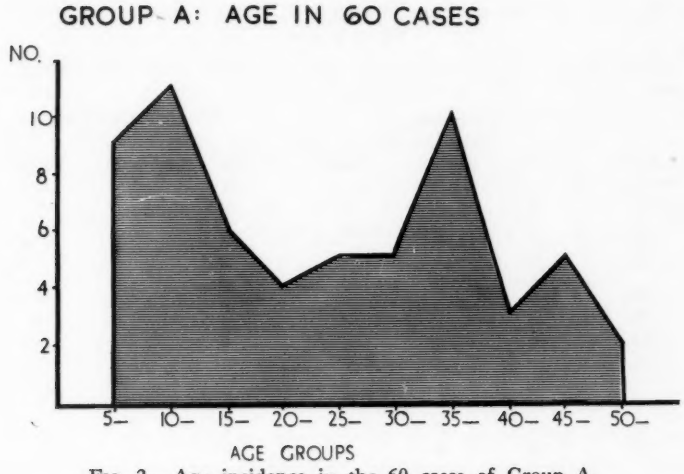

FIG. 2.—Age incidence in the 60 cases of Group A.

happens to be the major one. If the otitic cases, and 2 patients who clinically had cortical thrombophlebitis with raised intracranial pressure, are removed the initial peak is reduced (fig. 3). Of the 47 patients left

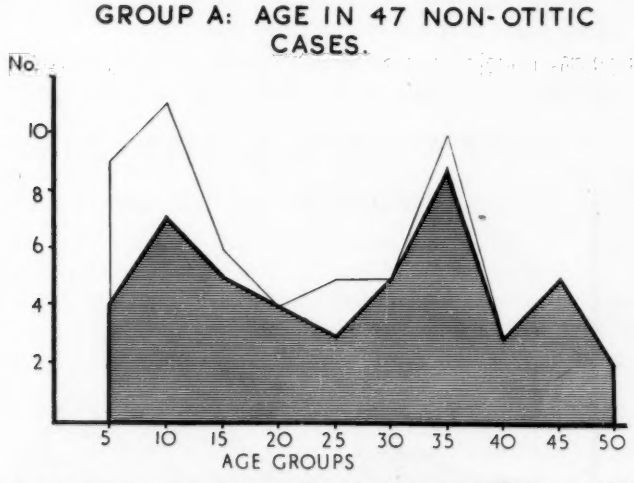

FIG. 3.—Age incidence curve after removal of otitic cases and 2 cases with clinical evidence of cortical venous thrombosis.

only 16 gave a history of antecedent infection or mild head injury—8 males and 8 females (Table VI). If these 16 cases are removed it is found that the first peak has all but disappeared. We are left with 31 "non-

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TABLE VI.—AGE AND SEX OF CASES WITH AND WITHOUT A HISTORY OF INFECTION OR HEAD INJURY

(Group A after exclusion of otitic cases and 2 cases of probable cortical thrombophlebitis).

	With history of Infection, etc.			*Without history of Infection, etc.*		
Age	*Male*	*Female*	*Total*	*Male*	*Female*	*Total*
0–	—	—	—	—	—	—
5–	3	4	7	1	1	2
10–	5	4	9	0	2	2
15–	0	3	3	1	2	3
20–	0	1	1	0	3	3
25–	2	1	3	0	2	2
30–	1	1	2	1	2	3
35–	2	2	4	0	6	6
40–	0	0	0	0	3	3
45–	0	0	0	0	5	5
50–	0	0	0	0	2	2

infective" cases, and the striking fact about these is that no less than 28 patients were females (fig. 4). One can thus distinguish three main groups:

(i) The otitic syndrome.

(ii) A group following infections and mild head injuries, affecting young males and females equally; and

(iii) a larger group without a history of infection and consisting almost exclusively of women, particularly in the fourth decade.

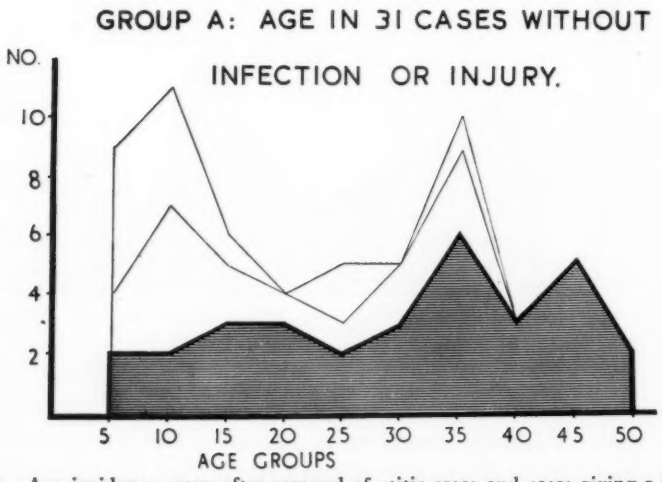

FIG. 4.—Age incidence curve after removal of otitic cases and cases giving a history of antecedent infection or head injury.

Antecedent Infection

The suggestion that, apart from the otitic syndrome, there may be two other conditions in the series becomes less convincing when the nature of the processes supposed to be causative is considered. In 16 cases the following conditions appeared to be related to the onset:

Sore throat	4
Coryza	1
Pyrexia of unknown origin	1
Asthma	1
Bazin's disease	1
Whitlow	1
Boil on thigh	1
Juvenile arthritis of hip	1
Caustic burn of eye	1
Mild head injuries	4

These conditions are so diverse that it is impossible to discern any common factor in them. When the cases were first classified the influence of pregnancy and miscarriage was not recognized. It may be argued that these conditions are as likely to be causative as is coryza; the transfer of four female cases from the "without infection" to the "with infection" category, however, still leaves a preponderance of females in the former. It will be shown later that benign intracranial hypertension can occur early in pregnancy as well as in the puerperium, and that there is no evidence that such episodes are due to infection or thrombosis.

Sinus and Cortical Thrombophlebitis

The small number of otitic cases in this series does not furnish clear evidence that lateral sinus thrombosis is the cause of the raised intracranial pressure. The evidence from the literature in support of this view has already been presented. Clinical evidence suggesting that cortical thrombophlebitis had spread from a thrombosed lateral sinus was present in only 1 of the 11 otitic cases with proven intracranial hypertension. The preponderance of right-sided otitis in this small series is not striking. Abducens palsies occurred in 7 of the 11 cases, being ipsilateral to the ear disease in 4, contralateral in 1 and bilateral in 2 instances (Table VII). Plain X-rays of the skull may sometimes demonstrate clearly which is the major lateral sinus (Plate I, fig. 5).

The object of the survey being to study cases of raised intracranial pressure of obscure origin, obvious cases of cortical thrombophlebitis were not included. In 2 cases, however, this was the probable diagnosis. In the remaining 47 cases the clinical evidence in favour of thrombophlebitis was meagre. While it is known that thrombosis of the superior longi-

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TABLE VII.—DATA FROM THE 11 OTITIC CASES

A. Otological Findings

Frank otitis on admission	6
History of earache only	5
Rigors	2
Mastoidectomy	
Normal mastoid	2
Purulent mastoid	3
Lateral sinus seen at operation	
Normal	2
Abnormal	2

B. Abducens Palsy in Relation to Side of Ear Disease

Side of ear disease	*Major lateral sinus as judged by groove on plain X-ray*	*Side of abducens palsy*
Right	Uncertain	Right and Left
Right	Uncertain	Uncertain
Right	Right	Nil
Right	Uncertain	Right
Left	Left	Right
Left	Left	Left
Left	Right	Left
Bilateral	Uncertain	Nil
Bilateral	Left	Left
Bilateral	Left	Nil
Uncertain	Left	Bilateral

TABLE VIII.—DURATION OF ILLNESS

(Onset to subsidence of papillœdema and/or symptoms)

	Number of cases			
Duration	*Otitic, and probable cerebral thrombophlebitis*	*Non-otitic with history of infection or head injury*	*Non-otitic without history of infection or head injury*	*Total*
0–4 weeks	2	1	0	3
1–3 months	2	7	6	15
3–6 months	4	3	7	14
6–12 months	4	0	9	13
1–3 years	0	3	7	10

tudinal sinus can cause intracranial hypertension without focal neurological signs (though almost invariably in such cases there is clouding of consciousness), it is reasonable to expect that in a large series of cases there will be some in which the postulated thrombosis has spread into cortical veins with consequent focal cerebral symptoms and signs and electroencephalographic changes; that there will be some patients who become comatose, and that some will die of the condition. The principal aim in collecting the present series was to find examples bridging the gap between the syndrome as it has been outlined and the classical and formidable clinical picture of superior longitudinal sinus thrombosis. If

the otitic cases, and the 2 that probably had cortical thrombophlebitis, are excluded, only one-third of the remainder gave a history of an antecedent infection or injury. Constitutional disturbance in the way of malaise was present in only 5; fever occurred at one or other stage in 3 cases, but was prolonged in only 1. Convulsions occurred in 4 cases, and were unilateral in 2. Focal sensory symptoms, on one or both sides, were present in 4 cases. Focal cerebral signs such as asymmetry of the tendon reflexes or slight weakness, were present in 8 cases. These signs were all minimal and ephemeral, though 1 patient, who had suffered from severe migraine, developed an homonymous quadrantic field defect. Slight inco-ordination of one limb was detected in 7 cases. It is quite possible that these equivocal signs were due to the pressure alone. Only 1 patient was drowsy, and she had neither fits nor focal signs. 2 patients noticed some swelling of the face at one stage, though neither had signs suggestive of cavernous nor sagittal sinus thrombosis. In 7 cases estimations of blood fibrinogen B were made, without positive results, and the method was abandoned.

Angiography was performed in 10 cases, and in 3 cases from Group B; taking all these cases together, satisfactory visualization of the superior longitudinal sinus was obtained in oblique views in 6 cases and in lateral views in 2; in 7 of these 8 cases there was no radiological evidence of obstruction of the sinus (Plate I, fig. 6). In 1 case filling of the posterior group of cortical veins was poor and direct sinography at another hospital is reported to have shown obstruction of the posterior third of the superior longitudinal sinus; this case was the only one in the series with prolonged fever, and 1 of 2 that developed thrombosis elsewhere in the body during or after the episode of intracranial hypertension. Direct sinograms were successful in 2 of 5 cases with no history of antecedent infection in which the procedure was attempted, and showed no evidence of obstruction (Plate II, fig. 7).

Electroencephalography may provide supporting evidence in favour of thrombophlebitis. Thus focal delta activity was present in the posterior temporal region on the side of the ear disease in 2 of the 4 otitic cases of which EEG records are available (fig. 8 overleaf); whereas amongst 24 non-otitic cases in which electroencephalography was performed a focal abnormality was detected in only 1, the patient who had migraine and a quadrantic field defect.

Allergy

That hypersensitivity may play a part in "toxic hydrocephalus" was suggested by Sheldon (1933) and McAlpine (1937, 1952), and their cases

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certainly support this view. In the present series, however, evidence that the condition may have an allergic basis is scanty. One patient was asthmatic, and her headaches began after a severe attack of asthma. One had Bazin's disease; she gave a history of several episodes of intracranial hypertension, the tentative diagnosis in one of them having been tuber-

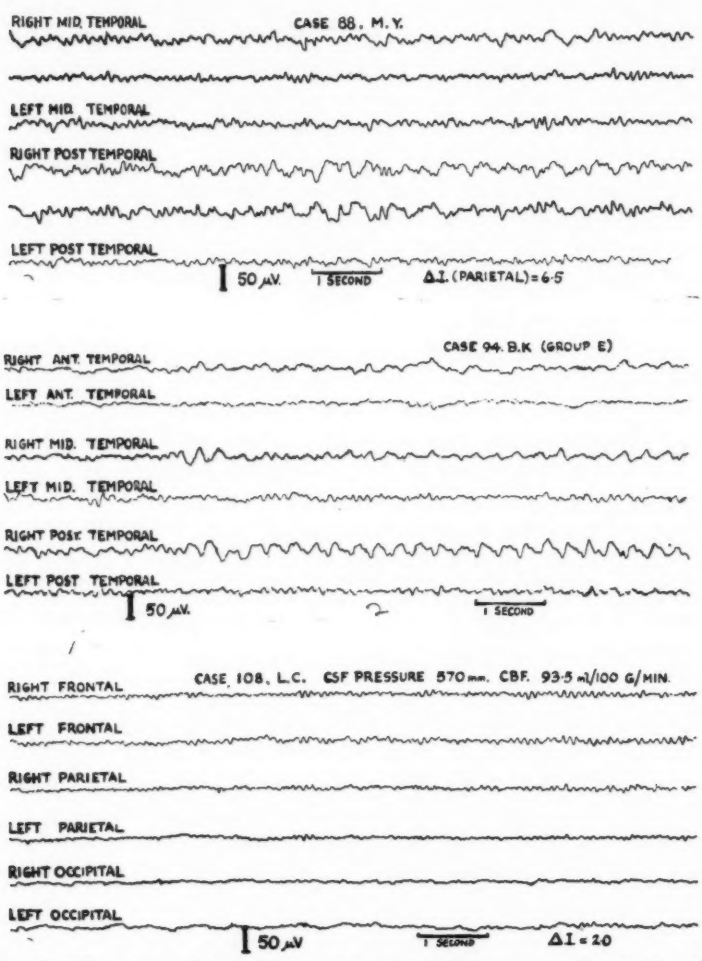

FIG. 8.—Electroencephalograms in otitic cases (upper two records) showing focal slow activity in the temporal regions above the affected ear; and in a non-otitic case (lowest record), demonstrating the typical absence of delta activity; the C.S.F. pressure was 570 mm. fluid.

culous meningitis. In 3 cases iridocyclitis preceded or appeared to initiate the condition; visual acuity was normal, and the intracranial hypertension lasted between five weeks and eight months.

Obesity and Disturbances of Uterine Function

From the presumably non-thrombotic cases two other factors emerge. Obesity was notable in only 1 otitic case, but was commented on in 22 of the remainder. Only 2 of these fat patients were males, and of the 28 females with no history of antecedent infection, 20 were fat; obesity was not restricted to females in the fourth decade. In 3 of these fat cases the illness was preceded by menorrhagia.

In 3 cases the episode of intracranial hypertension was associated with a miscarriage or stillbirth; in 1 of these the symptoms of raised intracranial pressure developed five weeks before the miscarriage, while in the other 2 they followed the miscarriage or delivery of a stillborn infant. If sinus thrombosis is the common explanation of intracranial hypertension (even when there is no disturbance of consciousness or clinical evidence of a cortical lesion) in the puerperium, it can less easily be invoked as the cause when the raised intracranial pressure develops during pregnancy. 4 patients were pregnant at the time of admission; symptoms of raised intracranial pressure had begun in the first month in 1 case, in the second month in 2 and in the fifth month in 1. 2 of these women were conspicuously obese; 2 gave a history of an earlier miscarriage; 1 gave a history of headaches and blurred vision in a previous pregnancy, and 1 had been found to have unilateral papillœdema in a previous pregnancy which had resulted in a stillborn infant. None of these 4 patients had any evidence of toxæmia or of crural thrombophlebitis, though 1 patient whose intracranial hypertension followed immediately upon a miscarriage later developed a white leg when the raised intracranial pressure had subsided. The 9 women in whom an episode of benign intracranial hypertension was associated with menorrhagia, pregnancy or miscarriage had produced between them 14 living children, of which 1 died of congenital heart disease after two-and-a-half months, 2 stillbirths and 8 miscarriages. It is difficult to avoid the suspicion that in these cases some endocrine disturbance with presumably a disturbance of electrolyte balance is in some way connected with the alteration of intracranial pressure. It is of some interest that a few instances of menstrual œdema associated with papillœdema have been reported in the literature (Thomas, 1933: McCullagh, 1941). The following case exemplifies the condition associated with pregnancy.

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Case 98. St. George's Hospital No. 147812.—M. A. D., female, aged 37. Admitted 4.6.51, discharged 17.6.51. Readmitted 9.7.51, discharged 27.7.51.

Family history.—One sister became obese after childbirth, and had a stroke at the age of 40, from which she made a good recovery.

Previous pregnancies.—The menarche was at 17. At the ages of 21, 22, 24 and 33 she had her first 4 children, and after each delivery she had a breast abscess. After the fourth child her periods occurred every three weeks; her weight was then 8 st. 6 lb. At the age of 35 she again became pregnant; at the third month she weighed 8 st. 13 lb. In the last three months she rapidly gained weight and became tired and out of breath, but she had no headaches. Parturition and lactation were normal, but she weighed 12 st. 8½ lb., and from then onwards she slowly gained weight. Her periods recommenced six weeks after delivery and had since remained regular and normal.

Previous illnesses.—Five years before admission she began to grow deaf in the left ear, tinnitus later appearing; this was attributed to otosclerosis.

Present illness.—Six months before admission she conceived, and she began to feel lethargic, which she had not done in any of her previous pregnancies. Four months before admission she began to have momentary stabbing pains in both temples, and her head sometimes felt as though it were swelling for a few seconds. Associated with these symptoms were little episodes of blurring of vision, and attacks in which objects would appear to move from side to side for about one second; these could be precipitated by sudden changes of posture. One month before admission, instead of the temporal pains she began to have dull heavy headaches at the vertex, coming on as soon as she stepped out of bed, and gone by the time she had dressed. When first admitted, in the fifth month of pregnancy, she was an obese woman with a blood pressure of 100/50; she had bilateral papillœdema of moderate degree, and a conductive deafness of the left ear with absence of the cold caloric responses. Her blood count was normal and she had no albuminuria. X-ray of the skull showed some thinning of the dorsum sellæ. She refused a ventriculogram and discharged herself. Headaches continued, and two weeks before her second admission she suddenly heard a rushing noise in both ears followed by a bang, which she at first thought was an explosion in her back garden; finding that this had not been the case she concluded that something had gone wrong inside her head, and although she had no more headaches she was readmitted to hospital.

On examination she was an obese young woman weighing 13 st. 8 lb., with a bloated appearance; there was no hypertension, œdema or albuminuria. Visual acuity was 6/6 in either eye; there was slight constriction of the left temporal quadrants and both blind spots were much enlarged. There was bilateral papillœdema of 3–4 D without hæmorrhages or exudates. Otherwise there were no abnormal neurological signs. The blood count, clotting time, bleeding time, urea and plasma proteins were normal. The EEG was abnormal only in that there was slight asymmetry of the alpha rhythm and there was a single short symmetrical burst of four-a-second activity; there was none of the slow activity usually associated with raised intracranial pressure. A right percutaneous arteriogram was normal, and in oblique views the superior longitudinal sinus appeared to be normal. The ventriculogram and ventricular fluid were normal. The lumbar pressure was 400 mm. fluid. She was discharged to a neighbouring hospital, where her progress was followed. She continued to have mild frontal and parietal headaches and in addition she began to have obscurations of vision. The disc swelling continued unchanged but there was no significant deterioration of vision. The pregnancy went to term and delivery was normal. When seen ten days later she was difficult to recognize, so much had she shrunk—her face was no longer bloated and she looked well; the papillœdema was subsiding but there were now a few small linear hæmorrhages round the discs.

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No other neurological abnormality could be found. Unfortunately a record of her fluid balance in the puerperium had not been kept. Since then she has remained well.

Head Injury

Occasionally an episode of inexplicable intracranial hypertension follows a mild head injury; this sequence occurred in 4 cases in the present series. The mode of onset, the clarity of the mind, the absence of significant neurological signs except papillœdema and perhaps a convergent squint, and the normal ventriculogram distinguish these cases clearly from examples of cerebral compression due to extradural, subdural or intracerebral bleeding, and from the rare but important instances in which a severe head injury with loss of consciousness is followed after an interval of hours or days by sudden and fatal intracranial hypertension, usually attributed to cerebral œdema. Nor does benign intracranial hypertension following a mild head injury resemble those cases of subarachnoid hæmorrhage in which papillœdema develops some days after the hæmorrhage and can obviously not be related to the actual volume of extravasated blood or to an intracerebral or subdural hæmatoma. In these cases of subarachnoid hæmorrhage with delayed intracranial hypertension there is usually some ventricular dilatation, and the condition resembles that induced experimentally by Bagley (1929). In the 4 cases of benign intracranial hypertension associated with head injury in this series the injury has been relatively mild and not associated with concussion or with symptoms in the early stages suggestive of any degree of subarachnoid bleeding. In 2, the interval between the head injury and the development of symptoms was a matter of days, and both patients were admitted within three weeks of the accident. One had a mild head injury six months before admission, and her symptoms dated from that time. In the fourth case the injury occurred eighteen months before admission. Both of the patients with the longer histories complained of vertigo on head movement in the early stages, and one also had tinnitus. An example of the acute syndrome is cited below.

Case 64. St. George's Hospital No. 115974.—R. R., male, aged 7½ years. Admitted 4.6.49; discharged 15.7.49.

Past illnesses.—Measles, chickenpox, whooping cough; tonsillectomy one year before admission.

Present illness.—Three weeks before admission a friend threw a brick at his head, striking him on the occiput; he fell but was not unconscious. Next morning he had pain in the forehead on bending, and transient mistiness of vision. Two days later severe frontal headaches began, and continued. Two weeks before admission he had nausea, vomiting and double vision twice, and he noticed that he could not see small things in his "comics." Five days before admission he was examined at the Hospital for Sick Children, Great Ormond Street, and was found to have a pulse-rate of 60, slight neck stiffness, slurred speech, bilateral papillœdema, intention

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tremor and dysdiadokokinesis of the left arm; and he was unable to balance on his left leg. He was accordingly transferred to the Neurosurgical Unit of St. George's Hospital.

On examination he was alert, with a pulse-rate of 52; there was a cracked-pot note on percussion of the skull. Visual acuity was not recorded, but the fields were constricted on confrontation; there was bilateral papillœdema without hæmorrhages or exudates. There was inco-ordination of both upper limbs, with dysdiadokokinesis on the left, and inco-ordination of the left leg; the left plantar response was extensor; his gait was unsteady with his eyes closed, with a tendency to deviate to the left. X-rays of the skull showed evidence of raised intracranial pressure. At ventriculography the dural tension was high; the fluid was contaminated with fresh blood and contained 3,200 red cells and 14 white cells per c.mm., and 30 mg. protein per 100 ml. The lateral ventricles were normal, but only the anterior part of the third ventricle was filled; myodil ventriculography two days later showed normal third and fourth ventricles. His visual acuity fell, and when seen thirteen days after admission it was R. 6/18, L. 1/60; he was alert and co-operative, and the right field on confrontation showed irregular constriction, with a central scotoma breaking out to the periphery; there was bilateral papillœdema with numerous hæmorrhages and widespread hard white exudates; the right pupil was larger that the left and almost fixed to light. Ocular movements were full and there was no nystagmus. The limbs were hypotonic and mildly ataxic; both plantar responses were extensor. His pulse rose slowly to 70.

Seventeen days after admission, despite his mental clarity and normal ventriculogram the posterior fossa was explored; the only abnormality found was a large cisterna magna. Almost one month after admission his visual acuity was R. 6/24, L. 6/12; he still had bilateral papillœdema, with some pallor of the discs now. On the day of his discharge there was a little swelling of the suboccipital decompression; visual acuity was unchanged; there was still gross constriction of the right field, with a very large blind spot; unfortunately scotometry was not carried out. The right disc was grey, swollen and broadened, the arteries were narrow, the veins dilated, and there were a few specks of exudate near the macula; the left disc was also greyish, but less swollen, the arteries were normal the veins slightly distended; there were no exudates. There were no other physical signs.

When reviewed four months later he was free from headaches and his vision had improved, although there was still some mistiness of the right eye. The suboccipital decompression was flat: visual acuity was R. 6/60, L. 6/9. While the left field was normal, the right was irregularly constricted; the blind spot was enlarged and there was an oval central scotoma. Reviewed again two years and four months after his illness, visual acuity was R. 6/60, L. 6/6. Careful scotometry was possible and demonstrated not only a very large blind spot on the right, but an irregular central and paracentral scotoma with a partly horizontal upper border which suggested that it might be part of an old nerve fibre bundle defect; the left field and blind spot were normal (Plate II, fig. 9). The left disc had returned to normal; the right was pale and sharply defined, though the lamina cribrosa was not visible.

Duration of the Illness

The duration of the illness is difficult to assess because the end-point is indefinite, and once a ventriculogram had proved negative and it was clear that vision was not failing, patients were discharged before papillœdema had subsided. Those cases in which the total duration is known approximately, i.e. from the onset of the first symptom suggestive of raised intra-

To illustrate article by John Foley
PLATE 1

FIG. 5.—Half-axial projection in a case of the otitic syndrome due to left-sided ear disease, showing the prominent groove of the left lateral sinus.

FIG. 6.—Oblique view of angiogram showing normal filling of the superior longitudinal sinus in a non-otitic case.

FIG. 7.—Normal direct sinogram in a non-otitic case.

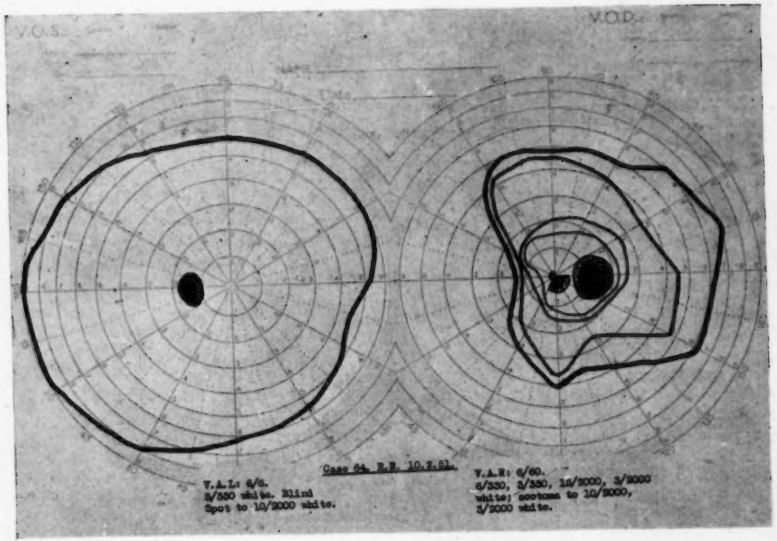

FIG. 9.—Visual fields in Case 64: benign intracranial hypertension following a mild head injury; unilateral visual failure due to a central scotoma resulting from papillœdema.

cranial pressure to the time when papillœdema or symptoms vanished, are listed in Table VIII (p. 27). The length of the illness is surprising, for previous reports, except that of Dandy (1937) have always suggested that this is a transient condition. The illness lasted more than a year in 10 cases and more than two years in 2. The commonest duration was between six and fifteen weeks. Contrary to expectation, some of the otitic cases were not of short duration, the symptoms in 2, for example, lasting thirty-four weeks. On the whole, however, the otitic cases and those in which intracranial hypertension followed an infection ran a slightly shorter course, and the 2 cases in the series with the shortest duration, namely three weeks, were both otitic.

Symptoms and Signs

Little is achieved by tabulation of the most common symptoms in the three groups, otitic, non-otitic with previous infection and non-otitic without such history. Headache, though common, was rarely severe, nor was vomiting frequent or persistent. Diplopia, due to unilateral or bilateral abducens palsies, was more common in the otitic cases (5 out of 11 otitic cases, 18 out of 49 non-otitic cases), and constitutional disturbance and drowsiness were also more common in the otitic group. The frequency of subjective disturbance of vision, other than diplopia, in the non-otitic cases is surprising, for it occurred in 22 of 47 cases, in the form of dimming, positive scotomata, or progressive failure; tinnitus and episodes of mild vertigo were also common in these cases and were probably due merely to very high intracranial pressure (Table IX).

Table IX.—Incidence of Symptoms in the Three Groups

Group	*Headache*	*Vomiting*	*Visual impairment, etc.*	*Diplopia*	*Tinnitus*	*Vertigo*	*Fits*	*Drowsiness*	*Dysæthesiæ*
Otitic and probable thrombophlebitis (13 cases)	10	4	1	5	2	2	1	3	0
Non-otitic with history of infection or head injury (16 cases)	14	6	8	7	2	2	2	1	1
Non-otitic with no such history (31 cases)	29	8	14	11	11	4	1	1	3

Papillœdema was present in all cases, but was in general more severe in the non-otitic. An evident ocular palsy on admission was more common in the otitic cases, as might be expected (Table X). In none of the otitic cases was there permanent visual impairment, though this occurred

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TABLE X.—INCIDENCE OF SIGNS IN THE THREE GROUPS

Group	*Papillædema*	*Defect of central visual field*	*Permanent impairment of vision*	*Squint*	*Nystagmus*	*Mild Pyramidal signs*	*Ataxia*	*Drowsiness*	*Neck stiffness*	*Constitutional disturbance, fever, etc.*
Otitic and probable thrombophlebitis (13 cases)	13	0	0	7	3	3	1	1	3	2
Non-otitic with history of infection or head injury (16 cases)	16	4	5	4	4	4	2	0	6	4
Non-otitic with no history of infection or head injury (31 cases)	31	2	7	9	6	5	3	1	7	2

in 12 of the non-otitic cases; central visual field defects were demonstrated in 6 of the non-otitic cases, and charts of these are available in 4. McAlpine (1937) and Davidoff and Dyke (1937) commented on the frequency and early development of visual failure in this condition in comparison with raised intracranial pressure due to tumours. Central scotomata have not been reported before: in general, they were responsible for early or sudden visual failure. In 12 of the 47 non-otitic cases there was ultimately some permanent impairment of vision; in 5 there had been a history of an antecedent infection or head injury. Visual impairment occurred fairly early in the illness in 7 of these 12 cases; visual impairment was as often due to central field defects (5 cases) as to classical secondary optic atrophy with progressive constriction of the field (5 cases); 1 patient had an homonymous quadrantic defect, and 1 had slight general depression. The degree of visual impairment was relatively slight in most cases, but 2 patients were almost completely blind in both eyes and 1 was almost blind in one eye. The mechanism of the production of central field defects will be discussed elsewhere.

THE CEREBROSPINAL FLUID

The cerebrospinal fluid is generally reported as being normal in this condition, but in the present series a slight pleocytosis was not uncommon. Leaving aside 2 otitic cases in which a frank sterile meningitis developed in the course of the illness, a pleocytosis above 5 per c.mm. in the lumbar fluid occurred in about the same proportion in the three groups. In the

non-otitic cases a pleocytosis could not be correlated with the acuteness of onset of the intracranial hypertension. There was no significant difference between the fluids in the non-otitic cases with a history of antecedent infection or head injury and the non-otitic cases with no such history, but it is noteworthy that there was a slight pleocytosis, after correction for contamination with blood, in 30 out of 40 ventricular fluids from the cases in these two groups. This finding is surprising, for it has not attracted comment before, and one may ask whether the cell counts were accurate, or whether any other factor could be responsible for the pleocytosis. The ventricular pleocytosis, albeit slight, is of some importance, for if thrombosis of the superior longitudinal sinus be the cause of the increased intracranial pressure it is difficult to see how this thrombosis, remote and downstream from the ventricles, can cause an increase in the number of cells in the ventricular fluid. A protein content of over 40 mg. per 100 ml. occurred in only 3 cases, of which 2 were otitic cases with a frank sterile meningitis and 1 was a case with no history of antecedent infection. It is pertinent to inquire whether raised intracranial pressure itself can cause a slight pleocytosis in the ventricular fluid. For this purpose the records of 100 consecutive cases with papillœdema due to space-occupying lesions in the posterior fossa were examined. Of these, only 13 had more than 5 cells per c.mm., while 17 had more than 10 mg. protein (10 of the 17 had neurofibromata). Dilatation of the lateral and third ventricles was absent in 7 cases, but in 5 of these (all acoustic neurofibromata) the protein was raised, and in 2 the cell-count was also raised. In all the other cases there was some degree of internal hydrocephalus; hydrocephalus was gross in 15 cases, but in only 2 of these was the protein content raised, while in 1 the cell count was also increased. Thus neither high pressure nor stretching of the ependymal walls appear to determine the presence of abnormal amounts of protein or cells. Presumably the amount of contaminating blood from the brain cannula was the same in the two groups; the cerebrospinal fluids of the tumour cases and of all but 6 of the cases of benign intracranial hypertension were examined in the same laboratory.

Thus a pleocytosis in the ventricular fluid, which has not received comment before, appears to bear no direct relation to the occurrence of infectious processes before the onset of the condition, and is difficult to account for on the basis of sagittal sinus thrombosis; furthermore it is not a response of the ventricular walls to high pressure *per se*. One must conclude tentatively that benign intracranial hypertension is the result of some low-grade infective process or that it is a condition of active œdema, or some other vascular disturbance, as the result of which an increased number of cells finds its way into the ventricles.

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Other Evidence as to the Cause of the Intracranial Hypertension

Setting aside the otitic cases, it is plain that in the remainder the evidence in favour of sinus thrombosis is scanty indeed. In most of the non-otitic cases we must therefore look for some other process. If formation of C.S.F. outpaced absorption the total volume of fluid must be slightly greater than normal and the ventricles should be slightly larger than normal. The two remaining factors in the intracranial system are the volume of the cerebral vascular bed and the mass of the brain tissue itself. Neither can be determined directly, but a change in the former should affect the cerebral blood flow. The relationship between intracranial pressure, cerebral blood flow and electroencephalographic abnormalities is a complex one which has yet to be clarified. While it is customary to regard diffuse symmetrical slow activity in the EEG as characteristic of raised intracranial pressure, it is well known that the delta activity itself is not directly related to the pressure and that in fact increased pressure without cerebral distortion is often associated with a normal record or with low-voltage fast activity (Stewart, 1941; Forster and Nims, 1942). In tumour cases, if delta activity is present, reduction of the pressure to normal does not abolish the slow waves; this can perhaps be correlated with the findings of Shenkin *et al.* (1948) that ventricular tapping reduces the pressure but does not elevate the cerebral blood flow. Stewart (1941) in his animal experiments distinguished two different forms of intracranial hypertension: "increased intraventricular pressure," i.e. obstructive hydrocephalus, and "generalized intracranial pressure," which he produced either by hydrostatic compression or by intravenous injection of distilled water, which causes (i) hæmodilution and diminished viscosity, (ii) increase in the volume of C.S.F., and (iii) cerebral œdema (Weed and Hughson, 1921). "Generalized intracranial pressure" Stewart found to be associated with an EEG of low amplitude and high frequency, and he concluded that slow activity is not due to either increased pressure *per se*, or to cerebral œdema. "Increased intraventricular pressure," on the other hand, was associated with delta activity, though it is of interest that in the early stages of rising pressure fast spiky waves appeared. Stewart regarded the slow activity as an expression of stress on the white matter; it could not be due to deformity of the ventricles, for ventricular puncture, which diminished the slow activity, abolished the stress, but could not alter the established deformity. It may be that the two forms of intracranial pressure which Stewart recognized differ in their effect upon the cerebral blood flow, for the ventricular obstruction with increase in the volume of C.S.F. will tend to occlude the intracerebral vascular bed and diminish the blood flow, as will most cerebral tumours; while the generalized form,

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associated with cerebral œdema and increased formation (and, necessarily, absorption under the higher pressure) of C.S.F. will be associated with a normal or elevated cerebral blood flow; the former state is accompanied by delta activity, the latter by fast activity similar to that which is found when CO_2 is breathed and both the cerebral blood flow and, consequently, the intracranial pressure, are raised.

Kety, Shenkin and Schmidt (1948), and others since then, have shown that in patients with cerebral tumours the blood flow falls with increasing pressure. It is of interest, however, that those patients of Kety *et al.* who showed a definite impairment of blood flow were all comatose; if the patients with tumours who were not comatose are considered alone, it is found that up to a pressure of about 450 mm. water there is no consistent fall in blood flow. It may thus be that the decline in cerebral blood flow commonly seen in tumour cases is in some way associated with the decline in conscious level and that both are only indirectly related to the intracranial pressure. Turning again for the moment to the EEG changes accompanying raised intracranial pressure, whatever may be the explanation, the amount of slow-wave activity in tumour cases can be correlated with the state of consciousness rather than with the pressure itself or with distortion of the ventricles; and the experiments of Stewart suggested that slow activity, when it appears, is not due to increased pressure *per se* or to cerebral œdema. Now alertness is one of the characteristic features of patients with what, for want of a better term, can be called benign intracranial hypertension; despite very high pressures the majority of the EEGs in the non-otitic cases of the present series were normal, and such slow activity as did occur could be correlated with age rather than with the pressure. If in these cases the very scanty slow

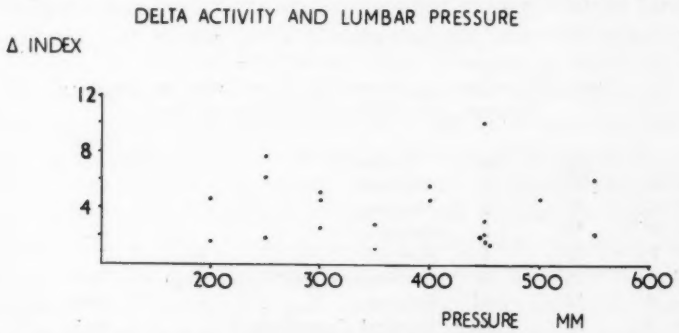

FIG. 10.—Relation between slow-wave activity in the electroencephalogram, expressed as the Delta Index, and lumbar pressure in cases of benign intracranial hypertension.

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activity is expressed as the "delta index" (Hoagland *et al.*, 1937) and plotted against the pressure it is found that with rising pressure there is no significant increase in slow activity (Table XI and fig. 10). It would not be unreasonable to expect normal values for cerebral blood flow in such cases.

TABLE XI.—C.S.F. PRESSURE AND DELTA ACTIVITY
(Expressed as Delta Index)

C.S.F. pressure mm. fluid	*Delta Index*	*Age*	*C.S.F. pressure mm. fluid*	*Delta Index*	*Age*
200–	1·5	36	450–	1·5	30
	4·5	53		1·5	40
				2·0	52
250–	7·5	11		1·5	49
	6·0	34		3·0	21
	1·7	22		10·0	19
300–	5·0	35	500–	4·5	32
	4·5	12			
	2·5	46	550–	2·0	36
				6·0	12
350–	1·0	45			
	2·75	7½	600–	28·5	5½
400–	4·5	37			
	5·5	35			

Estimations of the cerebral blood flow, using the nitrous-oxide technique, were made in 3 cases of benign intracranial hypertension unassociated with otitis, 3 cases with cerebral tumours, 2 with angiomas, and 5 with epilepsy or mild neurological disorders and no disturbance of intracranial pressure (Tables XII and XIII). The results from the miscellaneous cases are shown on the left in fig. 11; the range of normal is shaded, and in it fall 4 of the 5 anticipated normal controls; on the right side are the figures obtained in the 3 cases of benign intracranial hypertension, together with their lumbar pressures; not only are they above normal, but they lie in the

TABLE XII.—CEREBRAL BLOOD FLOW IN CASES OF ANGIOMA, TUMOUR, AND MISCELLANEOUS CONDITIONS

Case	*Age*	*Sex*	*Diagnosis*	*C.B.F. c.c./100 grammes/min.*
S. D.	19	F	Angioma	83·2
R. G.	45	F	Angioma	83·5
E. W.	50	F	Epilepsy	67·0
P. P.	32	F	Normal	53·3
H. N.	26	M	Choriomeningitis (recovering)	50·0
G. S.	19	M	Epilepsy	49·9
N. F.	30	M	Cerebral thrombosis	48·5
W. G.	37	M	Meningioma	43·4
S. B.	45	M	Glioma (coma)	27·5
E. R.	47	M	Glioma (coma)	26·0

TABLE XIII.—CEREBRAL BLOOD FLOW IN CASES OF BENIGN INTRACRANIAL HYPERTENSION

Case	*Age*	*Sex*	*C.S.F. pressure mm. fluid*	*C.B.F. c.c./100 grammes/min.*
100	45	F	250	73
109	19	F	490	76·9
108	36	F	570	93·5
„	(after 2 months)		215	44·6

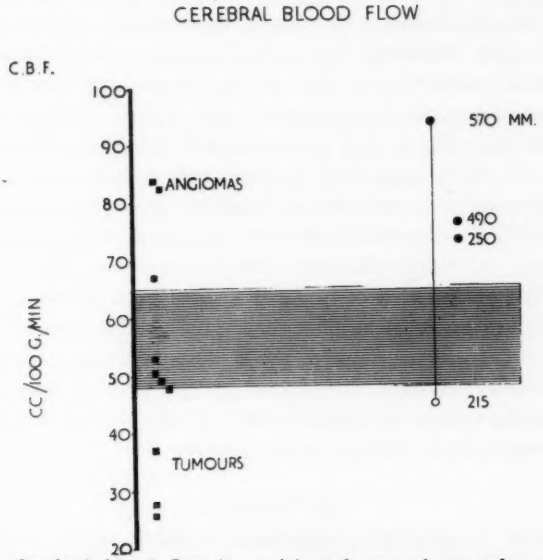

FIG. 11.—Cerebral blood flow in anticipated normal controls, angiomas and proven cerebral tumours (on the left) and in 3 cases of benign intracranial hypertension (on the right); the range of normal is shaded. The C.S.F. pressures are also recorded for the cases of raised intracranial pressure without tumour.

order of their cerebrospinal fluid pressures. It is of interest that in the case with the highest pressure and highest blood flow the estimation was repeated two months later when the pressure had fallen from 570 mm. to 215 mm. fluid; the cerebral blood flow was then just below normal.

Such scanty observations cannot constitute an explanation. Even if they are verified, the underlying mechanism still remains obscure. It is difficult to envisage an increase in cerebral blood flow occurring in the absence of increased CO_2 tension, hæmodilution or an increase in cerebral metabolism. Theoretically such an increase in flow might result from the opening up of vascular territories all of which are not normally open at one time, or from the opening of arteriovenous shunts; but the only arteriovenous shunts that have been demonstrated in the cranial cavity

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are in the choroid plexuses and are small (Millen and Woollam, 1953). Furthermore, as parallel estimation of cerebral arteriovenous oxygen difference were not made in all the cases it is possible that the high cerebral blood flow obtained by this method in this condition is apparent rather than real. The formula for the calculation of the cerebral blood flow involves a constant, the partition coefficient for nitrous oxide between brain and blood. This constant was determined with great care by Kety *et al.* (1948) and was found to be unity in dead and live brain equilibrated with nitrous-oxide mixtures; it was argued that it depended upon the physicochemical properties of the cerebral lipoids and that it could not alter under physiological circumstances. But because it happens to be the same in death as in life it does not necessarily follow that it cannot vary during life. A slight alteration in the physical properties of the brain lipoids would alter this constant and derange the equation; and such an alteration might be responsible for what we know, still only vaguely, as brain swelling. Although relatively rare, the condition outlined as benign intracranial hypertension is of interest because here, where we see raised pressure without tumour or hydrocephalus, may be found the key to many of the unsolved problems of intracranial dynamics, and in particular to those not very uncommon examples of cerebral tumour, usually meningiomas, where the rate of growth, size and site of the mass cannot account for the pressure on mechanical grounds alone.

Summary

(1) 95 cases of bilateral papillœdema without brain tumour or obstruction of the cerebrospinal fluid pathways have been reviewed. For the purpose of the present analysis 35 of these were discarded because, apart from the disc swelling, there was no objective proof of intracranial hypertension. In the remaining 60 cases with proven intracranial hypertension statistical examination shows that the ventricles are of normal size, and the theoretical significance of this is discussed. The ventricular size does not vary with the actual pressure or with the duration of the illness. The term hydrocephalus is inappropriate when applied to this condition.

(2) The 60 cases could be divided into three main groups: (i) otitic cases, in which thrombosis of the major lateral sinus is the probable cause of the raised pressure; (ii) a larger group in which there is no history of infection or injury, consisting almost exclusively of women, with a peak incidence in the fourth decade; and (iii) a smaller group in which the condition follows an infection or mild head injury, the sexes being affected equally and the age at onset tending to be lower than in the second group. Little evidence has been found that thrombosis of the superior longitudinal

sinus is responsible for the second or third groups. Obesity is a common feature of the second group, and there is also an association with pregnancy and miscarriage.

(3) Visual failure was not encountered in the otitic cases; it was relatively common, however, in the other cases, and it was as often due to central field defects as to secondary optic atrophy.

(4) Cases of the second and third groups, termed for convenience Benign Intracranial Hypertension, do not display in the electroencephalogram the slow activity commonly seen in cases with raised intracranial pressure due to cerebral tumours. There is some evidence that such slow activity, when generalized, is associated with a fall in the cerebral blood flow. A normal electroencephalogram in the presence of raised intracranial pressure may therefore indicate that the cerebral blood flow is normal. Estimations of the cerebral blood flow in three cases of benign intracranial hypertension showed it to be at the upper limit of normal.

I wish to express my indebtedness to Mr. Wylie McKissock, Mr. Valentine Logue and Dr. Denis Williams for permission to examine and follow up cases under their care, and to the Medical Research Committee of St. George's Hospital for a grant in aid of the work. I would also like to thank Miss P. Taves for her invaluable help in organizing the follow-up clinic.

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CARCINOMATOSIS OF THE MENINGES:
A Report of Three Cases

BY

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INTRODUCTION

CARCINOMATOSIS of the meninges is that rare form of intracranial metastatic disease in which the leptomeninges are diffusely invaded by a secondary carcinoma, and the condition both clinically and pathologically resembles a meningitis rather than a tumour. Intracranial tumours of all kinds are often disseminated along the cerebrospinal pathways, but usually there is an obvious tumour in the substance of the brain or cord and the leptomeningeal deposits take the form of discrete seedings. This is common in gliomas and has been fully described by Cairns and Russell (1931) and Polmeteer and Kernohan (1947). More rarely a nodular secondary tumour may spread throughout the leptomeninges, as in the cases described by Siefert (1902) and Humbert and Alexieff (1913). Occasionally such spread takes place from nodules in the dura (Hassin, 1919). Intracranial extension of a carcinoma in the form of a widespread carcinomatosis of the leptomeninges alone without the presence of a tumourous deposit is rare; Dixon, Kerr and Sharp (1946) reporting 2 such cases found only about 44 previous ones. The distinction between the two types of metastasis is not always clear-cut, since nodules may be microscopic or secondary to the meningeal invasion, and for this reason definite figures cannot be given. We have only accepted those cases in which there was no macroscopic intracranial deposit.

On account of the likeness to an infective meningitis the condition is sometimes referred to as carcinomatous meningitis. However, although this is a good descriptive term the lesion is purely neoplastic, and signs of meningitis are not always present, so that we prefer to call it carcinomatosis of the meninges. We have seen three cases, and their similarities are such as to present a distinct clinical and pathological entity. Previously reported cases confirm this impression.

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Case Reports

Case 1. *Summary.*—A woman, aged 57 had headache for two months, visual failure for one month, apathy and irritability. She became blind but the fundi remained normal. During the two months previous to death she had very severe headache, developed dementia, epilepsy, signs of mild meningitis, paralysis of sixth and seventh cranial nerves, generalized hypotonia and loss of reflexes. She died five months after the onset. Carcinoma cells were found in the cerebrospinal fluid.

Case 1.—A. W. (R.I. 171953), a married woman aged 57, was admitted to Stoke Mandeville Hospital on February 28, 1953, under the care of Dr. Ritchie Russell. She had had a dry irritative cough for about a year, with tiredness and loss of weight for a few months and progressive morning vomiting. Two months before admission she had been forced to give up shop work on account of headache. She had become irritable, depressed, and over-anxious, with loss of initiative and increasing apathy. Paroxysmal frontal and bitemporal headaches and later occipital headaches became increasingly violent, bursting and "gripping" in character; they prevented sleep, being exacerbated by lying down, and became so severe that she used to cry out. Throughout the month before admission her vision failed progressively, and she became slightly deaf. She had an epileptic fit on the day before admission.

On examination she was found to be an obese, plethoric woman, rational, with normal speech and no gross intellectual deterioration. She performed the 100–7 test in 70 seconds, but severe headache caused her attention and co-operation to be variable. She perceived but misnamed smells. There was a fluctuating loss of visual acuity: at times she was unable to count fingers accurately at six inches distance, but shortly after would do so correctly and locate a handkerchief on the floor. Her lack of acuity made it impossible to test her visual fields. The fundi were normal. The pupils were circular and equal, moderately dilated, and reacted only sluggishly to light and to accommodation—convergence. At times a paradoxical pupillary light reaction was observed. External ocular movements were full and there was no diplopia or nystagmus. Except for mild right-sided deafness and relative depression of both ankle-jerks, there was no other abnormality in the central nervous system. Sensation, apart from the special senses, was normal and remained so throughout her illness. Her gait was hesitant and slow because of poor vision. On admission her blood pressure was 250/150 but fell a few days later to 115/80. There was no evidence of cardiac failure, but throughout her illness rapid fluctuations in the blood pressure were noted, from 200/110 to 115/76. The chest and abdomen were normal and there was no glandular enlargement. She remained afebrile.

Three days after admission she developed slight neck stiffness. Two weeks later epileptic fits were observed, and for a few days she had several fits, despite heavy sedation. Most of the fits were focal, with twitching of the left side of the face and clonic movements of the left upper limb. Others were typical *grand mal* attacks, with unconsciousness lasting up to eight minutes, generalised rigidity and urinary incontinence, followed by drowsiness and severe occipital headache. She once had an aura of coloured lights. The whole head became tender. Vision deteriorated so that three weeks after admission she was virtually blind with fixed, dilated pupils. A slight left sixth nerve weakness and right lower motor neurone facial paresis developed. The limbs became hypotonic though motor power remained normal. She lost her abdominal reflexes and all her tendon-jerks. The plantar responses remained flexor.

At the end of March she was investigated in the Nuffield Department of Surgery, Radcliffe Infirmary, Oxford, in order to exclude a space occupying lesion. After

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her return to Stoke Mandeville Hospital there was a steady deterioration in her condition. She became doubly incontinent and completely disorientated, querulous, moaning, sometimes crying out with headache, sometimes singing and shouting. Epileptic attacks continued and she had neck stiffness with a positive Kernig's sign. There was a persistently high intracranial pressure. She lapsed into coma four days before death, developed broncho-pneumonia and died on May 14, 1953, four and a half months after the onset of neurological symptoms.

Investigations

The *cerebrospinal fluid* was at all times clear. Except when lumbar puncture was performed twice daily, the fluid was under much increased pressure, ranging from 240 mm. to 600 mm. of fluid with free rise and fall on jugular compression. On two occasions the cell count was less than one cell per c.mm. but otherwise the cells ranged from 11 to 15 per c.mm. with 7 to 10 polymorphs or lymphocytes and 4 or 5 carcinoma cells. These carcimoma cells were demonstrated on several occasions. The protein content ranged from 40 mg. to 80 mg. per 100 ml.; the sugar was 50 mg. per 100 ml. W.R. negative. Lange gold curve normal.

Skull X-ray showed erosion of the dorsum sellæ, with no enlargement of the pituitary fossa. Electro-encephalogram (March 17, 1953) showed no clear-cut alpha rhythm and there was slow spiky activity more marked posteriorly and more on the right than the left; two weeks later there were generalized episodic two cycles per second waves. Vertebral and right carotid *angiograms* were normal. An *air encephalogram* was first attempted by the lumbar route; air did not enter the ventricles but it revealed large, normally shaped cisterns. On ventriculography there was a pressure of 190 mm. of fluid and a symmetrical moderate dilation of the lateral, third and fourth ventricles with air passing freely into the cisterna magna.

Chest X-ray showed slight raising of the left side of the diaphragm with increased markings in the left upper zone. *Blood counts:* hæmoglobin was 16·6 grammes on admission but later fell to 12 grammes per 100 ml.; white blood cells ranged from 8,500 to 16,000 per c.mm. with a normal differential count and blood film. The *erythrocyte sedimentation* rate rose from 9 mm. on admission to 50 mm. four weeks later. The *urine* was sterile and *blood urea* was 23 mg. per 100 ml. The *blood pyruvate* level was normal.

Pathological Examination

Summary of necropsy (S.H. 4302/53, R.I.).—Bronchial adenocarcinoma. Diffuse carcinomatosis of the leptomeninges without macroscopic metastases in the brain. Bronchopneumonia.

Macroscopic examination.—The post-mortem was performed by Dr. H. J. Harris, Stoke Mandeville Hospital, who kindly sent us the brain. There was a small primary bronchial carcinoma (2·5 cm. diam.) in the left upper lobe. No macroscopic secondary deposits were found in any organ. There was a little terminal bronchopneumonia.

The *brain*, which was fixed by suspension in 10 per cent formol saline, was normal externally apart from some thickening and milky opacity of the leptomeninges. This was seen especially on the under aspect of the frontal lobes and over the parietal regions. There were no internal herniæ, but slight protrusions of necrotic brain tissue were present at the sites of the burr-holes. The optic nerves and optic chiasma appeared normal. Coronal slices, 1 cm. thick, through the fixed brain showed moderate symmetrical dilatation of the whole ventricular system, including the third ventricle and aqueduct of Sylvius. There was a slight degree of general cortical atrophy. No metastatic deposits were found in the brain substance. No evidence of demyelination was seen. Thin slices through the brain-stem and cerebellum showed no abnormality and no metastatic deposits were found here either.

Microscopic examination.—The primary tumour was predominantly an adenocarcinoma, the individual cells being columnar or cubical. There was a marked increase in fibrous tissue within the tumour area and some necrosis. The hilar lymph nodes were almost replaced by tumour.

Sections were examined of the medulla, pons, mid-brain, cerebellum, basal ganglia, external geniculate bodies, cerebral cortex (frontal, temporal and occipital regions), optic nerves, optic chiasma, choroid plexuses and pituitary.

The staining methods used were hæmatoxylin and eosin, hæmatoxylin and van Gieson, phosphotungstic acid hæmatoxylin, Weil's myelin stain, Holmes' method for nerve fibres, Best's mucicarmine, scarlet red and other fat stains.

These sections showed a widespread infiltration of the subarachnoid space by cells of an adenocarcinoma. The picture was most distinctive and could well be described as one of "carcinomatous meningitis," tumour cells covering the surface of the brain and dipping down into the sulci just as inflammatory cells do in an infective meningitis. Although almost the whole surface of the brain was involved the infiltration was particularly great in the sulci and especially in those of the cerebellum. Much of the surface of the brain was covered by a single layer of tumour cells forming an almost continuous sheet (Plate III, figs. 1 and 2), though in places the cells formed acini or were heaped up. The inner aspect of the arachnoid membrane was similarly covered by a single layer of tumour cells, and where vessels crossed the subarachnoid space they also were ensheathed by tumour cells (figs. 1 and 12). These cells were in general well differentiated, of columnar or cubicle type (fig. 2), with a tendency to form acini. No mucin was present. The appearance was quite different from the usual one seen in invasion of the subarachnoid space by a secondary carcinoma.

In many places the tumour cells spread into the brain as a sheath along the perivascular spaces of the penetrating vessels (fig. 4). However, the depth of such penetration was not great and wherever tumour cells were seen within the substance of the brain they were cuffing the blood vessels. This perivascular penetration was most marked at the crests of the folia in the cerebellum, the tumour cells in places reaching into the granular layer but not as far as the white matter. The diaphragma sellæ was invaded by the tumour and well formed acini were present in the posterior lobe of the pituitary. The ventricular surfaces were free of tumour and the choroid plexuses were not heavily invaded, though histologically there was at least one small area invaded.

The optic nerves were surrounded by tumour but without any marked penetration into the substance (fig. 3); both nerves showed severe degeneration.

There was severe degeneration with much neutral fat present in the brachia pontis without any striking degeneration of the cerebellum. Sections of the lowest level of the medulla did not show ascending degeneration from the cord, and the pyramidal tracts were normal.

Case 2 *Summary.*—A woman aged 68 became virtually blind within two weeks. During the next month she developed anosmia, impairment of ocular movements, and lost her reflexes. Clinical and radiological signs of a bronchial carcinoma appeared, and she died five months after the onset. Carcinoma cells were found in the cerebrospinal fluid.

Case 2.—Mrs. R. H. (R.I. 123296), aged 68, was admitted to the Churchill Hospital, Oxford, on May 1, 1950, under the care of Dr. Ritchie Russell on account of failure of vision during the previous five weeks.

She had been feeling tired for a year and had lost about two stones in weight over the past few months. Ten weeks before admission to hospital she developed a severe cough and went to bed. At that time also her legs felt so weak that she

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had difficulty in walking properly. Her eyes felt "strained" on reading. In March 1950, she noticed gradual failure of vision, affecting all parts of the visual fields, but on March 31 her visual acuity, corrected, was normal (6/6) in both eyes. During the next two weeks, however, there was a fairly rapid loss of vision so that on April 18, 1950, her visual acuity was less than 6/60 bilaterally, apparently due to central scotomata. For two weeks before admission she had had slight supra-orbital headache and tenderness.

On admission she looked fairly fit, but had obviously lost weight recently. Speech and intellectual functions were normally preserved. She had only faint perception of light in both eyes with fixed irregular pupils; the fundi showed no marked abnormality and all cranial nerves were normal. In the motor system, the only abnormalities were diminution of the following tendon-jerks: right biceps, left triceps, right knee and ankle jerks, and a doubtfully extensor right plantar response. Tone, motor power and co-ordination were normal, as were all sensory modalities. Blood pressure was 120/70 and the pulse was regular. There was an apical systolic murmur. No other abnormal physical signs were found.

Lumbar puncture on May 3, 1950, showed a clear cerebro-spinal fluid under a pressure of 60 mm. of fluid with free rise and fall on jugular compression. The protein content was 80 mg. per 100 ml., W. R. negative, and Lange 1, 000, 000, 000. There were 34 cells per c.mm. Typical lymphocytes, polymorphs and macrophages were seen, and in addition cells containing nucleoli which were thought to be carcinoma cells.

Skull X-ray suggested decalcification of the dorsum sellæ. *Other investigations* showed Hb. 12 grammes per 100 ml. W.B.C. 9,000 per c.mm. Urine sterile with no abnormal contents.

On May 4, 1950, she developed a left basal pneumonia; the X-ray appearances suggested a neoplasm. A week later there were physical signs of fluid at the left base with collapse above and the X-ray showed that the left main bronchus was occluded. Aspiration produced only a few milli/litres of blood-stained fluid, in which no malignant cells were seen.

She was discharged home on June 1, 1950, four weeks after admission; her main complaint was still blindness, but physical signs had changed in certain respects. She had developed bilateral anosmia and a moderate degree of bilateral optic atrophy. She had impairment of ocular movements both upward and downward. The palate moved rather poorly and there was slight deviation of the tongue to the left on protrusion. All her tendon-jerks had now become sluggish. The right plantar response had remained doubtfully extensor. In view of the blindness with scattered neurological signs but without evidence of intracranial tumour, associated with a suspicious chest X-ray and the presence of abnormal cells in the cerebrospinal fluid, the most likely diagnosis was thought to be a carcinomatosis of the meninges secondary to a pulmonary neoplasm. The possibility of a secondary deposit compressing the optic nerves or of a toxic neuritis as the cause of the blindness was considered.

She died at home three months after the onset of neurological symptoms.

Pathological Examination

Summary of necropsy (P.M. 305/50. R.I.).—Adenocarcinoma of bronchus, with widespread metastases. Diffuse secondary spread of carcinoma throughout the sub-arachnoid space.

Macroscopic examination.—A firm white tumour, showing no macroscopic necrosis, was found arising near the origin of the main bronchus of the left lower lobe and spreading out peripherally. Numerous secondary deposits were present in the right lung and one in the left adrenal. There was diffuse spread over the pleura, peritoneum and diaphragm. Otherwise the organs were normal.

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The *brain* showed no external abnormality apart from some thickening and opacity of the leptomeninges and slight generalized cortical atrophy; the optic nerves and chiasma appeared normal. After fixation by immersion in 10 per cent formol saline, the cerebrum was cut into coronal slices 1 cm. thick. No metastatic tumour nodules were seen, nor was any area of demyelination visible macroscopically. Slices through the brain-stem, cerebellum and spinal cord also failed to show any macroscopic metastases, although there was a minute focus of erosion into the cerebellar cortex (*see below*). The cerebral ventricles showed slight generalized dilatation, in keeping with the degree of cortical atrophy. The ependyma was smooth and normal throughout and the choroid plexuses also appeared normal. The leptomeninges on the other hand were thickened and grey over the posterior surface of the spinal cord, over the cerebellum, around the pineal and in the tela choroidea, the appearances suggesting a mild chronic meningitis.

Microscopic examination showed a primary bronchial carcinoma of predominantly cubical and columnar cell type, in which there were numbers of well formed acini (fig. 5). There was much fibrous tissue in some areas and here the adenomatous structure was best seen. Elsewhere minute foci of necrosis were present. The adenomatous structure of the tumour was seen even more clearly in the various secondary deposits. Microscopically one ovary was found to be involved in the general peritoneal spread.

Sections were made from the following regions of the central nervous system: parietal, occipital, and temporal areas; basal ganglia, brain-stem, cerebellum, optic nerves, optic chiasma, spinal cord and choroid plexuses. The staining methods used were the same as in Case 1. The subarachnoid space was found to be lined by a continuous sheet of tumour cells in all the sections examined. These cells were mostly cubical (fig. 7) or sometimes columnar. Frequently there was only a single layer (fig. 6) though in places acini were present and occasionally the cells were heaped up (fig. 8). There was no mucin. A number of multinucleated and giant cells were seen; mitoses, though present, were not frequent. The tumour cells showed a remarkable tendency to spread along surfaces and here and there they formed a cuff around a penetrating vessel, passing for some distance into the substance of the brain. This penetration was most noticeable in the cerebellum (fig. 6), where at one point folia were eroded to a depth of 2 mm. No nodular deposits of tumour were found in the brain and the only region where tumour cells penetrated to any depth was in the basal ganglia where they were found along the penetrating vessels for a considerable distance. There was a small deposit of tumour in the choroid plexus. The upper aspect of the pituitary was invaded through the diaphragma sellæ as part of the general subarachnoid spread. The posterior spinal nerve roots and the fifth and eighth cranial nerves were ensheathed and actually invaded by neoplastic cells. The optic nerves were encased in tumour (fig. 11) though there was little penetration into these nerves even along the blood vessels. There was severe degeneration of both optic nerves.

Case 3. *Summary.*—A woman aged 55 complained of severe throbbing headache for three months, but no abnormality was found at the first neurological examination. Nine days later she became blind, and developed paralysis of the facial and ocular muscles, generalized hypotonia and loss of tendon-jerks. She became partially demented, and died four months after the onset. Carcinoma cells were found in the cerebrospinal fluid.

Case 3.—Miss O. S. (R.I. 121640/51), aged 55 years, had worked as head of a secretarial college. She had suffered from attacks of migraine for 30 years but had otherwise been well until January 1950, one year before the present illness, when she had had a transient weakness of dorsiflexion of the left foot. She had had no other serious illnesses. In January 1951 she began to have attacks of

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headache which were so disabling that she had to give up her work. These attacks consisted of severe throbbing, at first associated with pain in the neck and occipital region and later with a sense of pressure and giddiness.

Between January and March 1951, the headaches became more severe and she had two attacks of loss of consciousness.

On March 20, 1951, she was admitted to the Churchill Hospital, Oxford, for investigation under the care of Dr. Ritchie Russell. On admission she showed no neurological abnormality other than some generalized weakness of the right leg, but within a few days she developed diplopia. Lumbar puncture at this time gave a clear cerebrospinal fluid under a pressure of 60 mm. with a protein content of 45 mg. per 100 ml. and 19 cells per c.mm. of which 7 were polymorphs and 12 lymphocytes. X-rays of the skull were normal.

On April 9th there was an abrupt deterioration in her condition. The headache which had lessened returned, there was rapid loss of vision, and she complained that her right leg "felt dead." The headache became so severe that the patient was rapidly demoralized by it. This made examination difficult, but there seemed to be no intellectual impairment. Her vision was reduced to light perception only in the left eye, with a fixed pupil; while with the right eye she could count fingers and had preserved a sluggish reaction to light. There was now a bilateral external rectus palsy and limitation of upward eye movement; also a mild left facial weakness.

By April 11 she had developed retention of urine and had generalized muscular hypotonia, with loss of tendon-jerks and some sensory impairment in the right lower limb. Plantar responses remained flexor. Lumbar puncture gave a cerebrospinal fluid pressure of 100 mm. with a protein content of 80 mg. per 100 ml. and 35 cells per c.mm., of which 2 were polymorphs and 33 "atypical lymphocytes."

On April 13 she was transferred to the Nuffield Department of Surgery, the Radcliffe Infirmary, under the care of Mr. Pennybacker for further investigation. She had no papillœdema, but the disc margins were blurred, and, in addition to the other external ocular palsies, downward movement was now also restricted. There was an ill-sustained nystagmus and, as before, some mild left facial weakness. The other cranial nerves were normal. The heart and lungs were normal on physical examination and the chest X-ray was clear. In the pelvis there was a firm fixed mass in the pouch of Douglas, suggesting a malignant ovarian tumour; no other mass was palpable in the abdomen. Superficial lymph nodes were not enlarged.

Lumbar puncture in April showed some large atypical cells which were thought to be malignant.

E.S.R. was 4 mm. in the first hour. Urine examination showed no abnormality other than some albumen.

During the next ten days (April 13–23) the headache was very severe and she became noisy and confused at night. She had a variable hypertension, her blood pressure ranging from 140/100 to 200/140. Following hypertonic enemata the intracranial pressure fell, the headache lessened, the blood pressure fell to 110/80, her vision improved and she was then thought to have a binasal field defect. There was a temporary improvement in the eye movements.

Her condition steadily deteriorated and she died at home on May 5, 1951, five months after the onset of neurological symptoms.

Pathological Examination

Summary of necropsy (P.M.253/51, R. I.).—Adenocarcinoma of the colon with metastases in both ovaries, the epicardium, para-aortic and iliac lymph nodes; diffuse carcinomatosis of the leptomeninges. Bronchopneumonia.

Macroscopic examination.—At the rectosigmoid junction the large bowel was constricted by a carcinomatous mass in its wall. There was no free fluid in the

abdomen. Both ovaries were much enlarged (10 x 10 x 5 cm. and 10 x 5 x 5 cm.) lobulated and fleshy with gelatinous cysts; there were no adhesions, the surface being smooth and glistening. The para-aortic and iliac lymph nodes and those of the transverse meso-colon were invaded by homogenous grey-white tumour tissue. There was some collapse at the lung bases, with early bronchopneumonia. A small abcess was present in the left kidney. Otherwise the organs appeared normal.

The *brain* showed no abnormality apart from a slight gelatinous thickening of the leptomeninges over the base. The spinal cord, on the other hand, was covered by an extensive gelatinous exudate which was suggestive of a chronic meningitis. After fixation in 10 per cent formol saline the cerebral hemispheres were cut into coronal slices 1 cm. thick. The ventricular system was normal, no deposits of tumour being seen on the ependymal surface or on the choroid plexuses. No secondary deposits were seen in the brain substance. Thin slices were made through the brain-stem and cerebellum, but no secondary deposits were seen here or in the spinal cord.

Microscopic examination.—The primary tumour in the large intestine was an adenocarcinoma of signet-ring-cell type. It was infiltrating the submucosa and muscle coat. In its less differentiated part giant cells and multinucleated cells were seen, as were some mitoses. The secondary deposits in lymph nodes and replacing the ovaries showed a similar cell type. A small deposit of tumour was found in the epicardial fat penetrating slightly into the myocardium.

The following regions of the nervous system were examined microscopically; occipital, parietal and frontal lobes, optic nerves, optic chiasma, optic tracts and external geniculate bodies, basal ganglia, mid-brain, pons, cerebellum, medulla and three regions of the spinal cord. The choroid plexuses were also examined. The staining methods used were the same as in Case 1.

In this case, as in the previous two cases, the subarachnoid space was found to be lined with tumour cells (figs. 9 and 10), though no discrete metastases were discovered in the substance of the nervous system. The third, fifth, ninth and tenth cranial nerves and some of the spinal nerve roots were sheathed in tumour tissue, and in some instances the neoplastic cells had actually invaded the nerves. In this case the pattern of the tumour cells in the subarachnoid space differed from that in the previous examples and there was also more fibrosis of the arachnoid. Instead of forming a continuous sheet the tumour cells tended to be arranged in clumps, or to lie separately, sometimes rather sparsely over the cerebrum. In some places well marked acini were formed, but nowhere was there the continuous single layer of cells, which was so striking a feature in the other two cases. Penetration of the brain along the perivascular spaces was also less marked, except in the cerebellum. As in the earlier cases the optic nerves were heavily coated with well differentiated tumour cells. Mucin was present in the tumour cells.

Discussion

Amongst the cases in the literature of carcinomatosis of the leptomeninges without nodular metastases, which showed features similar to those described, we have found the following of particular interest:

A characteristic case of carcinomatosis of the meninges secondary to carcinoma of the lung was described by Eberth in 1870. He did not, however, recognize the metastatic nature of the meningeal lesion and attributed it to an unassociated co-existing "endothelioma" of the meninges. His patient had in common with ours severe headache and

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intellectual deterioration, followed by an internal strabismus. Saenger (1901) described a case in which one year after mastectomy for carcinoma a patient developed headache, vomiting, diplopia and deafness. Microscopically dense accumulations of carcinoma cells were found in the pia over the convexity of the brain, at the base around the roots of the cranial nerves, and ensheathing the blood vessels in the subarachnoid space. Lilienfeld and Benda (1901) described a patient with carcinoma of the stomach who, apart from gastric symptoms, had a paraparesis with absent knee-jerks, followed four weeks later by paralysis of the face and the right arm. At post-mortem there was an extensive carcinomatosis of the pia arachnoid, with no tumour masses in the brain. In the spinal cord the carcinoma cells had penetrated along the glial septa, the blood vessels and the posterior roots. There was destruction of some of the cells in the posterior root ganglia. Scholz (1905) described two cases of carcinoma of the stomach with a macroscopic appearance of meningitis, but on microscopy this appearance was found to be due to a diffuse spread of carcinoma in the subarachnoid space. Rehn (1906) had a case in which polyneuritis of the legs was the predominant feature. At autopsy a carcinoma of the lung was found, with carcinomatosis of the basal and spinal meninges, widespread degeneration of fibres in the spinal cord, and involvement of nerve roots. Knierim (1908) reported a case of carcinoma of the stomach with headache, blindness, deafness and loss of reflexes. Macroscopically there was slight opacity of the basal meninges, and the optic nerves were said to be swollen. Microscopically tumour cells were found in the subarachnoid space and were particularly thick over the optic chiasma. Knierim discussed the possible routes of invasion and concluded that there was spread along the peripheral nerves from the peritoneal cavity. Stadelmann (1908) reported secondary infiltration of the leptomeninges from a carcinoma of the stomach. He found carcinoma cells in the cerebrospinal fluid, and this appears to be the first published case with this finding. Hoffmann (1909) in reviewing his cases of intracranial secondaries draws particular attention to three with leptomeningeal spread. One of these with a primary in the œsophagus was very similar to our cases, whilst the other two had nodular cerebral metastases as well. Lissauer (1911) reported a patient with carcinoma of the cæcum who developed symptoms suggestive of a posterior fossa tumour, together with rapidly progressive paralysis of the cranial and spinal nerves. It was only on microscopic examination that infiltration of the pia arachnoid by carcinoma cells was found. Schwarz and Bertels (1911) saw carcinoma cells in the cerebrospinal fluid, obtained by lumbar puncture, and at autopsy found "meningitis carcinomatosa" covering the

brain, but without nodular metastasis. A complete post-mortem was not performed, but the primary appeared to be in the stomach. Bertrand and Aronson (1921) described a case, clinically much like ours, with epilepsy, headache and rapid onset of blindness. Although they considered it to have been primary carcinomatosis of the leptomeninges this was undoubtedly a secondary invasion. Walshe (1923) described a woman whose physical signs were confined to the left eye—sixth nerve palsy, blindness and primary optic atrophy. At post-mortem a primary tumour was not found, but the basal leptomeninges and cranial nerve roots were infiltrated by an adenocarcinoma, thought to be derived from the gut. Moorhead and Wigham (1926) reported a case of diffuse carcinomatosis of the leptomeninges, the origin of which was uncertain, since only the brain and spinal cord were examined. Parker (1927) reported a similar case from a primary lung carcinoma. In the same year Cornwall reported a case originating from a carcinoma of the stomach and pathologically similar to our third case; but clinically there was marked papilloedema and signs of meningitis. In this case the carcinoma cells penetrated in the perivascular spaces for some distance into the brain substance. Kasanin and Crank (1933) described a case with pathology similar to Boyd's (1925), in both of which there was a diffuse melanoblastoma of the leptomeninges, without macroscopic nodules in the brain and secondary to a malignant melanoma of the skin.

In the last twenty years there have been a number of further cases reported. Greenfield (1938) described a patient aged 58 with a bronchial carcinoma who presented with a dementia and at autopsy showed a characteristic pathological picture. Microscopically there was diffuse carcinomatous infiltration of the leptomeninges spreading into the cortex along the small vessels. The case of Alpers and Smith (1938) was remarkable because, as in Rehn's (1906) case, there was severe infiltration of the spinal meninges with relatively little invasion of the cerebral meninges. The posterior aspect of the cord was more heavily infiltrated than the anterior aspect, as in an infective meningitis. The clinical picture was one of polyneuritis. Allen and Mercer (1942) described two cases, one of them coming on eight years after mastectomy for scirrhous carcinoma, both presenting with headache and both developing cranial nerve palsies. Dixon, Kerr and Sharp (1946) reported two cases in both of which the primary tumour was in the stomach, one of which was diagnosed by the finding of malignant cells in the cerebrospinal fluid. Since then Hamrick and Mason-Hohl (1948) have reported a case from a primary adenocarcinoma of the breast, and in the same year Willis added a case of his own secondary to a carcinoma of the pancreas. Alajouanine, Boudin,

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Nick and Contamin (1950) had a case which presented as a polyneuritis, in which the primary was not found, but was thought to be in the prostate. Ramse (1951) added a further case from a gastric carcinoma. Willis (1952) gives a brief review of the whole subject of secondary tumours of the leptomeninges.

Carcinomatosis of the leptomeninges is difficult to diagnose with certainty on account of the lack of localizing signs and the protean nature of the disease. The three cases reported in this paper, however, had certain features in common, as did a number of the previously recorded cases quoted above.

In each of our patients there was a period of vague ill-health attributable to the growth of the primary neoplasm and lasting between three months and a year before the onset of neurological symptoms. This is not always so, and a number of the reported cases have presented with neurological complaints without any previous ill-health.

Symptoms of nervous disease appeared rather suddenly and progressed on the whole rapidly. Our patients were dead within three to five months after the neurological symptoms had developed; most of those reported died within four months although occasional patients have survived for up to eighteen months.

Headache is usually prominent and has often been the first symptom. This was so in more than half the cases reported, but those patients who showed much involvement of the spinal meninges presented with low back pain or pain in the limbs (Alpers and Smith, 1938; Alajouanine *et al.*, 1950.) In others the first symptoms were visual disturbances, mental deterioration or fits. The headache is frequently severe and intractable and may be described by the patient as bursting or throbbing, affecting any part of the head, and often associated with pain at the back of the neck. This headache may be so severe that the patient becomes demoralized, abusive and noisy. Associated with the headache there may be an extreme tenderness of the scalp. So marked was this tenderness in our Case 1 that a diagnosis of temporal arteritis was for a time considered.

Although headache is often so prominent and severe a symptom, it is not invariable as shown by our Case 2, who never had more than slight headache and tenderness.

In Cases 1 and 3 the headache fluctuated in severity, perhaps due to intermittent increase in intracranial pressure, since exacerbation of headache was associated with a rise of blood pressure, and relieved by rectal magnesium sulphate. Exacerbation of the headache was often accompanied by deterioration of vision. Both patients had a remarkably labile

blood pressure. On the other hand, the patient with only mild headache had a normal blood pressure, and no apparent variations in her visual loss.

Both our patients with disabling headache showed profound disturbances of intellectual functions. In Case 3 this could be attributed in part to the continuous beating sound in the head. For three weeks before death this patient was incoherent and in acute distress from the headache, but was still rational when the headache eased. Case 1 however progressed to a definite dementia; at first restless confusion alternated with drowsiness, while six weeks before death she became noisy, irrational and disorientated. Mental changes have been a feature in a considerable number of the cases previously reported. Dementia, maniacal outbursts and mutism have all been noted.

The most striking clinical feature of our patients was visual failure. Almost complete loss of vision developed within five weeks in Cases 1 and 2, while Case 3 became blind in forty-eight hours. Apart from pallor of the optic discs in Case 2, the fundi were within normal limits. Visual failure, amounting in some cases to complete blindness, has been a feature in almost a third of the cases recorded by other authors, and at least one patient (Walshe, 1923) presented as a primary optic atrophy. It seems usual for the discs to be normal though there may be papillœdema (Bertrand and Aronson, 1921).

There was paresis of several cranial nerves in our 3 patients, who all showed oculomotor palsies, or impairment of conjugate movements, in addition to the blindness and loss of pupillary reactions. Case 1 had a unilateral sixth nerve palsy. Case 2 had anosmia and impairment of vertical ocular movement. Case 3 had ptosis, unequal pupils, a bilateral sixth nerve paralysis and loss of upward ocular movement. Cases 1 and 3 both had unilateral facial palsies. In the literature cranial nerve paralysis was the most consistent single feature; it frequently involved the eye muscles, whilst facial paralysis and deafness have also been noted. Case 2 had also a partial paresis of the palate which seems to be unusual.

Our patients had generalized hypotonia with universal loss of tendon-jerks and abdominal reflexes. The plantar responses were flexor. Most reports which we have seen mention loss of tendon-jerks. Case 3 alone had a mild weakness of one lower limb but there was no cutaneous or deep sensory loss. Some patients, however, present a picture of polyneuritis with pain in the back and limbs and motor and sensory disturbances (Alajouanine *et al.*, 1950).

Case 1 had numerous focal and generalized epileptic fits during the last two months of life and there was a history of two fits in Case 3 during

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the last six months of life. Fits have been reported in the literature but relatively rarely.

The majority of patients reported have shown signs of meningeal irritation, but this was only a transient feature in our 2 cases with severe headache. In these it was surprising that there was so little meningeal irritation, in spite of the extensive infiltration of the meninges with carcinoma cells, and chronic meningitis was not considered in the differential diagnosis.

The cerebrospinal fluid in our cases showed nothing diagnostic apart from the presence of malignant cells. The pressure was much increased only in Case 1, on whom lumbar puncture had to be performed twice daily. The protein content was only moderately increased, ranging from 40 to 80 mg. per 100 ml. while the total cell count though slightly raised was never above 35 cells per c.mm., indeed on two occasions it was within normal limits. Usually about a third of the cells were polymorphonuclear but in each case carcinoma cells were also found by Dr. Spriggs and illustrations of the cells from Cases 1 and 3 may be seen in his paper (Spriggs, 1954, Cases 7 and 1). The diagnosis is difficult to make with certainty and the presence of carcinoma cells in the cerebrospinal fluid is the one specific finding, although it does not exclude the presence of nodular metastases. Stadelmann (1908) appears to have been the first to describe malignant cells in the cerebrospinal fluid in this condition, but a number of later authors have also found them, e.g., Schwarz and Bertels (1911), Dixon *et al.* (1946). Spriggs (1954) gives an excellent review of the literature on malignant cells in the cerebrospinal fluid and describes their distinguishing features. Considerable experience is often needed to recognize the cells and it is probable that cases are overlooked on this account.

Pathology.—The pathology of these 3 cases was similar, the most striking feature being the almost normal naked-eye appearance associated with an extensive histological lesion.

The only macroscopic abnormality in each case was a slight thickening of the cerebral leptomeninges, such as might pass unnoticed, but with rather more thickening over the cord where the appearance suggested a meningitis. There was some generalized ventricular dilatation with a corresponding mild cortical atrophy. No macroscopic tumour deposit was found in the dura, the brain, or, in the 2 cases examined, in the cord. Microscopically, on the other hand, the carcinomatous infiltration was most extensive, covering much of the cerebrum and almost the whole of the brain-stem and cerebellum. It took the form of a thin sheet of cells, often a single layer, on both the arachnoidal and pial surfaces of the

subarachnoid space (figs. 6 and 12). In places there were well-formed acini. The meninges in the 2 cases with bronchial carcinoma (Cases 1 and 2) were indistinguishable in appearance, the cells being columnar or cubical (figs. 2, 7 and 12). These cells showed a marked tendency to spread along any available surface (figs. 1, 3 and 4). In this way the adventitia of the blood vessels in the subarachnoid space were surrounded by carcinoma cells (figs. 1 and 12) which continued on the penetrating vessels as a perivascular cuff for a short distance into the substance of the brain (fig. 4). The meninges in the third case, with a primary in the colon, were rather different in appearance, the cells being mainly of the signet-ring type and with more tendency to clump together (figs. 9 and 10); but here too the meningeal infiltration was extensive and diffuse, there was acinar formation but little penetration into the brain. The bronchial carcinomas were not mucus-forming; the colonic carcinoma was.

The histological appearance of carcinoma of the bronchus is often not uniform throughout, but individual tumours show a greater or lesser degree of differentiation. In our cases the adenomatous component was particularly well developed, both in the primary (fig. 5) and in all the secondary deposits. It is of interest that the majority of reported cases have also been adenocarcinomas. We believe that this type of carcinoma has a particular tendency to metastasize to the brain as a diffuse leptomeningeal spread. This is suggested by the fact that of over fifty bronchial carcinomas which we have seen with intracranial metastases in only three have the metastases been adenocarcinomas. Two of these are the cases reported here, and the third also showed the same features. In this latter case the primary tumour was an "adenocarcinomatosis" of the lungs, and there was the same diffuse spread in the leptomeninges. This case has not been included because there were also innumerable minute deposits in the brain, many of them microscopic. Examination of these deposits suggests that they are essentially perivascular collections of cells and it seems probable that they originated as ingrowths from the meninges especially as the majority of them were near the surface of the brain, Heinemann's case (1911) appears to fall into this category. This case has often been referred to as an example of carcinomatosis of the meninges, but we have excluded it on account of the lesions within the thalamus.

The spread of tumours by the cerebrospinal pathways is not at all uncommon (Cairns and Russell, 1931) but in most cases it is secondary to a macroscopic nodule in the central nervous system and consists of a greater or lesser number of isolated seedings. Diffuse spread over the surface of the brain is sometimes seen from a glioma and also in malignant melanomas (Boyd, 1925; Kasanin and Crank, 1933).

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The difficulty of finding a small nodule was well shown by Rich and McCordock (1933) in tuberculous meningitis, when by cutting brains very finely they demonstrated in the majority of cases tuberculomas which would have been missed by a routine examination. Equally small nodules may have been overlooked in the cases reported here; however, not only have we scrutinized the brains with this in mind but the histology of these 3 cases is distinct.

The mode of entry into the subarachnoid space is not clear; several possible routes have been suggested by previous authors. Knierim (1908) thought that in his case, a gastric carcinoma, it was by retrograde growth along the lymphatics of the peripheral nerves. Heinemann (1911) believed there could have been infiltration through lymphatic spaces in the base of the skull from cervical lymph nodes. Rehn (1906) recognized both invasion along the nerve roots and entrance from the blood-stream as a possibility. Willis (1952) commenting on the reported cases considered that the route of invasion was still undecided. In our cases only a few of the nerve roots were examined histologically, but macroscopically there was no evidence of invasion along them. Two of the cases (1 and 2) had metastases in the choroid plexus. Since, however, these were only microscopic and since the ventricular surfaces were free of tumour this was probably not the main portal of entry. Direct invasion of the meninges from the blood-stream seems to us probable.

A feature of great interest is the degeneration of the optic nerves leading to blindness. The optic nerves were completely surrounded by tumour cells in Cases 1 and 2 (fig. 3) and almost completely in Case 3, but our sections showed there was little penetration of the nerves themselves. Such penetration as was present was perivascular, in contrast to the direct invasion and destruction in other cranial nerve roots. It is possible that there was severe invasion of the optic nerves within the orbit, where they were not examined, but this seems unlikely. There is no evidence that degeneration was caused by interference with the vascular supply. It is possible that the carcinoma cells produced some "toxic" substance. This view is supported by the fact that in Case 1 there was neutral fat near the surface of the optic nerves, and there was also some degeneration of the superficial white matter in the pons. Several degenerative conditions of the central nervous system have been reported in association with carcinoma elsewhere in the body (Denny-Brown, 1948; Brain, Daniel and Greenfield, 1951; Henson, Russell and Wilkinson, 1954; Heathfield and Williams, 1954) and in the present cases the degeneration of the optic nerves may be related to these.

Summary

(1) A clinical and pathological study of three cases of carcinomatosis of the leptomeninges is reported.

(2) The main clinical features were numerous cranial nerve palsies with blindness in all 3 cases, severe headache, and a varying degree of dementia.

(3) Carcinoma cells were demonstrated in the cerebrospinal fluid in each case.

(4) The main pathological features were the extensive surface spread of carcinoma cells in the subarachnoid space, and severe degeneration in the optic nerves, with no discrete nodular deposit in the nervous system. All three primary tumours were adenocarcinomata.

(5) A comparison of our cases with those in the literature suggests that there is a recognizable clinical picture. The pathology of many previously reported cases is strikingly similar.

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LEGENDS TO PLATES

PLATE III

FIG. 1 (*Case* 1).—Showing the pia mater in a sulcus covered by a continuous single layer of carcinoma cells, which also surround the vessels in the subarachnoid space. (H. and van G. × 46.)

FIG. 2.—To show the columnar type of the carcinoma cells lining the subarachnoid space in Case 1. (H. and van G. × 660.)

FIG. 3 (*Case* 1).—Optic nerve covered by a sheet of tumour cells, which do not penetrate it. The nerve shows some degree of degeneration. (H. and van G. × 25.)

FIG. 4 (*Case* 1).—Cuffing of a penetrating vessel in the cerebral cortex by carcinoma cells. (H. and E. × 120.)

PLATE IV

FIG. 5 (*Case* 2).—Section of lung showing adenocarcinoma of the bronchus. (H. and E. × 172.)

FIG. 6 (*Case* 2).—Section of cerebellum showing carcinoma in the leptomeninges and penetrating into a folium along the vessels. (H. and E. × 46.)

FIG. 7 (*Case* 2).—Well-defined adenocarcinoma in the subarachnoid space showing similarity to primary tumour. (H. and van G. × 172.)

FIG. 8 (*Case* 2).—Heaped up carcinoma cells in a cerebral sulcus. (H. and van G. × 46.)

PLATE V

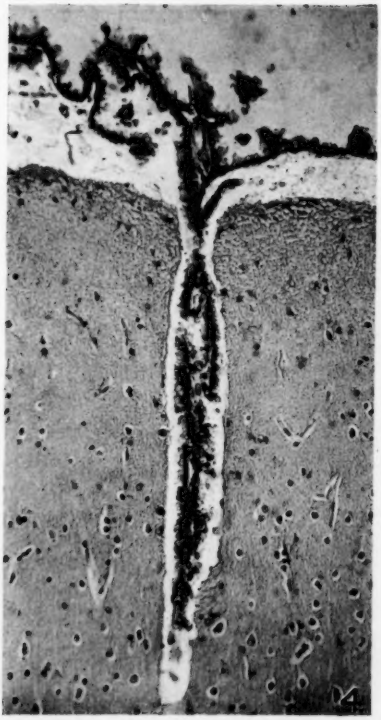
FIG. 9 (*Case* 3).—Showing carcinoma cells of the signet-ring type in the subarachnoid space of the cerebellum. Note the carcinoma cells around the penetrating vessel. (H. and van G. × 120.)

FIG. 10 (*Case* 3).—Tumour cells on the surface of the cerebrum. Note acinar formation at one point. (H. and van G. × 163.)

FIG. 11 (*Case* 2).—Surface of optic nerve showing tumour cells forming acini, but with very little penetration. (H. and E. × 150.)

FIG. 12 (*Case* 1).—Columnar cell carcinoma covering both sides of the subarachnoid space and ensheathing the vessels. There is well marked acinar formation. (H. and E. × 226.)

PLATE III



To illustrate article by Mariella Fischer-Williams, Frances D. Bosanquet and Peter M. Daniel.

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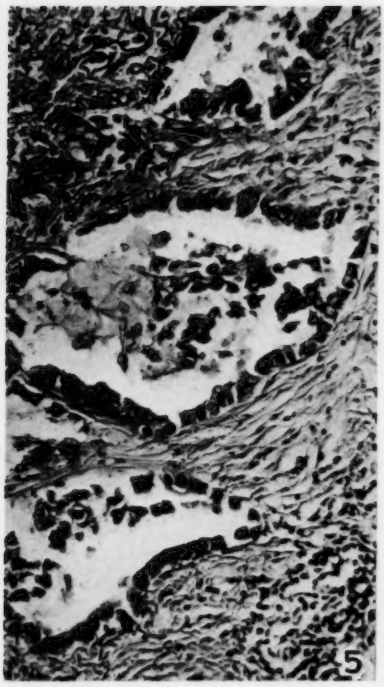
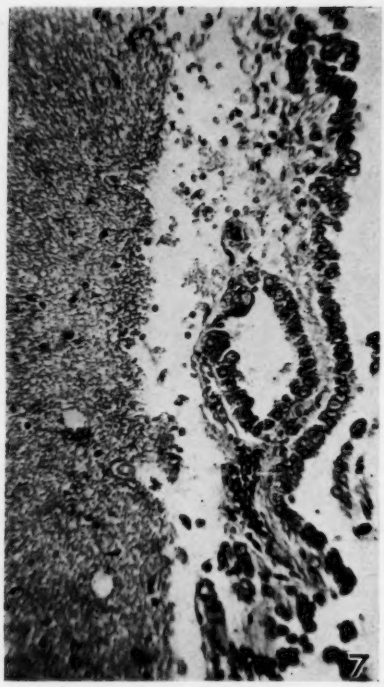
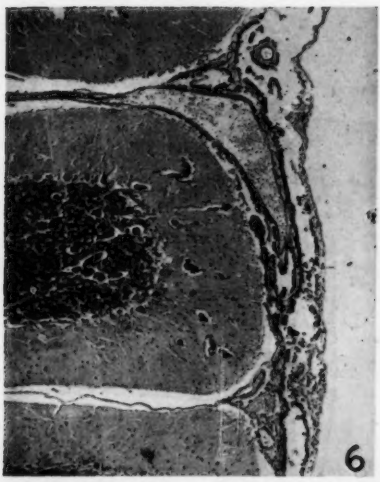
PLATE IV







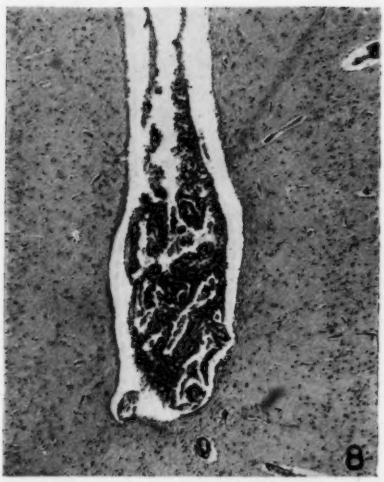


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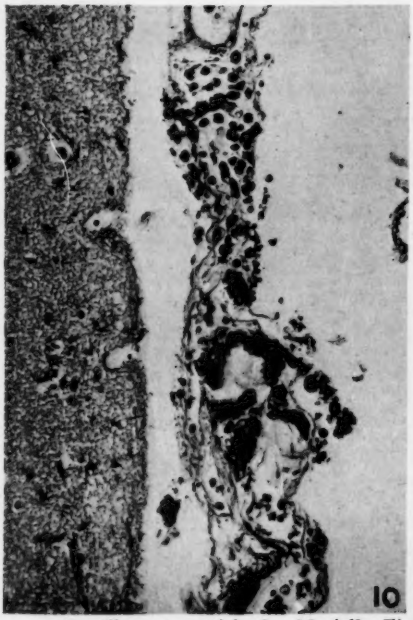
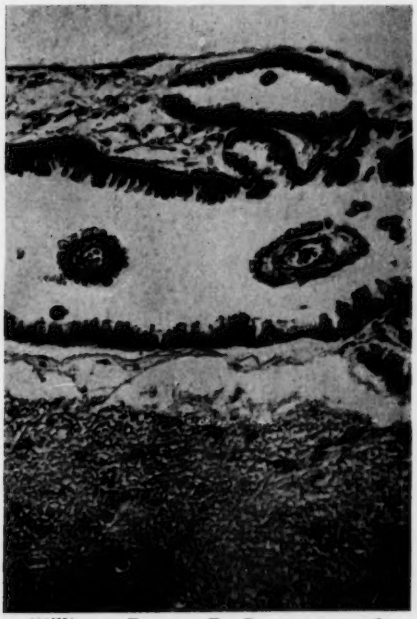
PLATE V





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THE NATURE AND CLINICAL SIGNIFICANCE OF PIGMENTS IN THE CEREBROSPINAL FLUID

BY

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THE clinical fact that the subarachnoid and subdural fluids may become discoloured during the course of intracranial disease is widely appreciated and it is remarkable that the pigments responsible for coloration have not been studied systematically. The difficulties which may have thwarted an investigation of this type have now been largely eliminated by the development of photo-electric spectrophotometers of high precision, particularly the newer self-recording instruments such as those designed by Hardy, Cary and Beckman. Furthermore, microchemical methods are now available for the analysis of small quantities of pigment in the cerebrospinal fluid.

In view of the paucity of specific data on the subject it seemed desirable, therefore, to seek further information concerning these pigmentary changes by the application of these techniques; and we set as our objective the determination of the nature of the pigments in cerebrospinal fluid, the part they play in the production of xanthochromia and their clinical significance. In the interest of making the examination of cerebrospinal fluid pigments clinically useful we have introduced three simple qualitative chemical reactions and have compared their results with those yielded by spectrophotometry. Although not specific, these methods, the benzidine, the van den Bergh and potassium cyanide tests, were found to indicate the presence or absence of oxyhæmoglobin, bilirubin and methæmoglobin, respectively. In the present report qualitative data of the absorption characteristics in the visible spectrum (400–700 millimicra) of coloured cerebrospinal fluids are presented. In the future, quantitative determination of these pigments may yield useful clinical information.

Absorption spectrophotometry, one of the principal techniques employed in this study, is the measurement of light intensity in different regions of the spectrum after its transmission through an absorbing medium. In 1873 Vierordt established this technique as a means of study-

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ing body fluids and directed his attention particularly to oxyhæmoglobin and its related pigments. Heilmeyer (1932) summarized the accumulated knowledge of these substances in an authoritative and comprehensive monograph. These investigators did not direct their attention to the cerebrospinal fluid even though, being normally clear and colourless, it is an ideal medium for absorption studies. The small amount of work that has been done in this field has been confined to the near ultraviolet rather than to the visible spectrum.

The limitations of the method of spectrophotometric analysis must be recognized. Substances differing in chemical structure may have identical spectral characteristics in a particular region of the spectrum, and, conversely, the same chemical molecule may show a variety of spectral absorption curves, depending upon the solvent in which it is placed. Thus, an aqueous solution of neutral methæmoglobin and an ethyl alcoholic solution of acid hæmatin are practically indistinguishable in the visible spectrum. Moreover, the presence of serum protein in an aqueous alkaline solution may shift the wave-length of maximal absorption of bilirubin 30 millimicra toward the red end of the spectrum. For these reasons one should refer to pigments in the cerebrospinal fluid as having the absorption spectra of oxyhæmoglobin, bilirubin or methæmoglobin. Without more specific definition, it must not be inferred from spectrophotometric analysis alone that these pigments are chemically identified. The spectrophotometric technique, at least with older types of apparatus, is also cumbersome, and precision instruments are not available in most hospitals.

Previous Work

That the cerebrospinal fluid occasionally contained yellow pigment was discovered soon after the lumbar puncture was adopted as a clinical procedure. In 1902 Milian and Chiray proposed the term, "xanthochromia" to describe the supernatant cerebrospinal fluid in subarachnoid hæmorrhage. A year later Froin reported 3 cases in which the cerebrospinal fluid was yellow, coagulated massively and contained an excess of lymphocytes. It was thought that these and similar cases were due to a syphilitic meningitis. Blanchetière and Lejonne (1909) described a case of cord tumour with a coagulated yellow spinal fluid but without a lymphocytosis. A year later Nonne described 6 cases of cord tumour with increase in spinal fluid globulin and without lymphocytosis. This cerebrospinal fluid formula thereafter was called "Nonne's compression syndrome" and an increase in protein accompanied by xanthochromia and spontaneous coagulation was termed "Nonne-Froin syndrome."

Greenfield and Carmichael (1925) suggested that in subarachnoid hæmorrhage the degree of colour intensity in the supernatant fluid was important in estimating the date of onset. Within two to four hours they noted a slight yellow tinge to the supernatant fluid which at the end of twenty-four hours became a yellow colour. It was their belief that hæmoglobin was the pigment responsible for the maximal yellow colour found between the sixth and tenth days. However, they had difficulty identifying any pigments with the hand spectroscope and by the ordinary chemical tests for bile pigments.

The observation that lumbar cerebrospinal fluid below a tumour compressing the spinal cord was xanthochromic was verified by many neurologists. No attempt to determine the nature or the mechanism of formation of xanthochromic fluid was made, however, until 1936 when Robinson and Miller produced experimental compression of the spinal cord in dogs and recovered xanthochromic high protein fluid. It was presumed that this coloration was due to venous congestion from the dilated veins which they found below the level of obstruction. Benzidine tests of the xanthochromic fluids were negative and no further attempt was made to identify the pigment.

Bilirubin has been demonstrated in the cerebrospinal fluid of jaundiced patients by many investigators (Klein and Szentmihályi, 1932; von Gündell and Jacobi, 1926; De Castro, 1931; Berman, Lapham and Pastore; With, 1945; and Amatuzio, Weber, and Nesbitt, 1953). Klein and Szentmihályi have stated that the intensity of the xanthochromia depends upon the duration of the icterus. De Castro proposed a minimal threshold of 30 Ehrlich units (15 mg. per 100 ml.) at which bilirubin enters the cerebrospinal fluid from the blood. In addition, he thought that cerebrospinal fluid bilirubin levels were always less than 1 Ehrlich unit (0·5 mg. per 100 ml.) and did not change with the intensity of jaundice. Berman, Lapham and Pastore recently found xanthochromia and detectable amounts of bilirubin in all 20 jaundiced patients studied. In one of their patients, jaundice was of only twenty-four hours' duration. Their data suggested a relationship between the level of the bilirubin in serum and spinal fluid. Others have been unable to find this relationship (Klein and Szentmihályi, 1932; Amatuzio, Weber and Nesbitt, 1953).

Stern (1939) analysed the chemical constituents of cysts of the brain and found that they contained the same substances as transudates from the blood. He concluded that cystic fluid was a transudate of serum from vessels of increased permeability within the lesion. In a study of the chemical constituents of cerebral cysts, Cumings (1950) obtained bilirubin values between 0·01 and 1·25 mg. per 100 ml. in 33 of his cases. There

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was no direct relationship between the total bilirubin, albumin or total protein. He agreed with Stern that this fluid was formed by a process of transudation from blood vessels.

Methods

Samples of fluid were examined as soon as possible after spinal, ventricular or subdural puncture. After a cell count, the centrifuged supernatant fluid was transferred under sterile conditions to an absorption chamber, 10 mm. in depth. A continuous spectral density curve was obtained between 400 and 700 millimicra on the Carey constant-recording Spectrophotometer. This instrument was used for obtaining most of the continuous density curves but for a few samples the Spectrophotelometer[1] was employed. Both instruments have a satisfactory resolving power isolating narrow spectral band widths between 400 and 700 millimicra. On the Carey constant-recording type of instrument, however, a curve can be obtained in about five minutes, whereas, using the Spectrophotolometer[1] at least an hour or more is required to obtain the readings, make the calculations and plot the curve on graph paper.

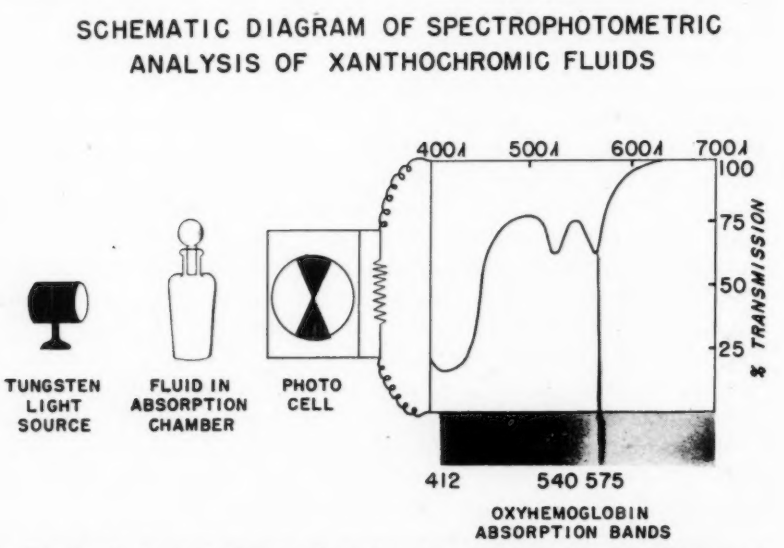

Fig. 1.—A schematic diagram illustrating the principles of the spectrophotometric technique in the analysis of xanthochromic cerebrospinal fluids. The light source transmits a beam through a quartz absorption chamber. The transmitted light enters the photo-electric cell where the potential change causes the moving needle on the automatic recorder to trace a curve on the graph. The absorption peaks at 412, 540, and 575 millimicra correspond to the bands on the spectrum.

[1] This instrument is manufactured by the Central Scientific Company, Chicago, Illinois.

With the light source constant, the net density is measured by converting light waves into electrical energy by means of a photo-electric cell (fig. 1). In this way a continuous absorption spectrum is obtained and it was unnecessary to plot density at specified wave-lengths. The amount of light transmitted through the chamber enters the photo-electric cell and the difference in electrical potential between the coloured fluid and a water standard produces a net density measurement which is automatically recorded on a moving graph. As the density of a solution increases arithmetically, the transmission of light decreases logarithmically: $d = \log \frac{1}{T}$ (Beer's Law). For any pigmented fluid the absorption bands appear at the same wave-length despite differences in concentration. It is the wave-length where maximal absorption occurs, therefore, that permits qualitative determinations, and the degree of absorption at any given wave-length that makes quantitation possible (fig. 2). When two or

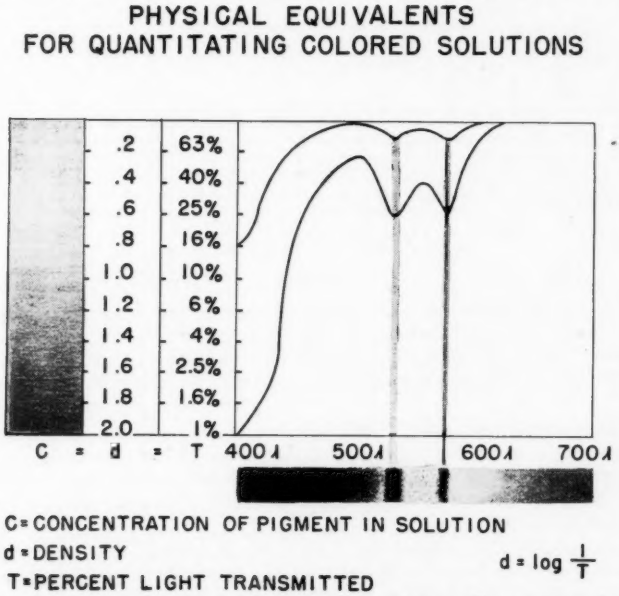

FIG. 2.—As the concentration of a pigment in solution (C) increases, the density (*d*) increases arithmetically while the per cent of light transmitted (T) decreases logarithmically. The lower curve demonstrates a more concentrated solution of oxyhæmoglobin than the upper curve. Despite differences in concentration, absorption for identical pigments is at the same wave-length but at different densities.

more pigments are in the same solution, plateaux and other modifications may occur, since the slope of the curve of a pure pigment may be markedly altered by the absorption characteristics of additional pigments.

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The characteristics of the spectral density curves of the four pigments found in this study of fluids were the following:

(1) *Oxyhæmoglobin.*—The parent pigment has a deep absorption band in the blue end of the spectrum at about 415 millimicra, a broader band at 540 millimicra, and a narrower band at 575 millimicra, the absorption of the last two bands being approximately the same density. The slope of the curve then falls sharply, so that at 600 millimicra there is almost maximal transmission (fig. 3).

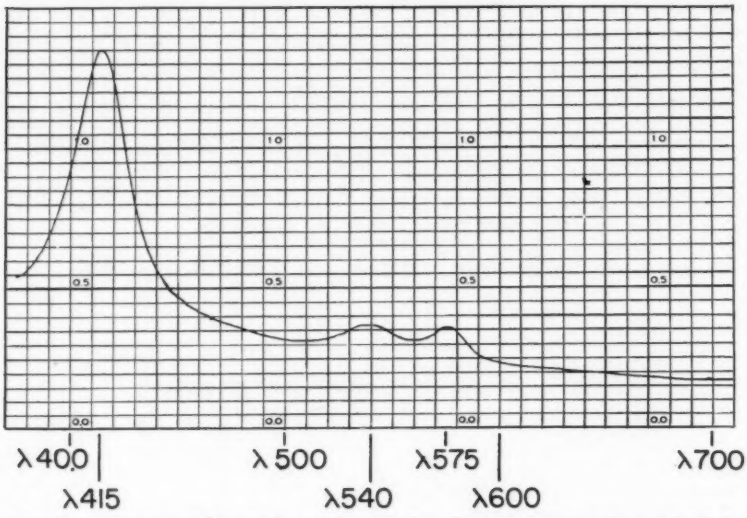

FIG. 3.—A spectrophotometric tracing of the absorption curve in a spinal fluid from an early case of subarachnoid hæmorrhage. Each vertical line equals 10 millimicra. The numerals on the graph refer to the density reading. The curve is typical for oxyhæmoglobin with absorption at 412, 540 and 575 millimicra.

(2) *Bilirubin.*—The iron-free derivative of hæmoglobin has a very steep slope in its absorption curve, falling sharply from 430 to 480 millimicra in the blue end of the spectrum to 540 to 580 in the green-yellow portion of the spectrum. In general, when the protein is elevated, the maximal absorption for bilirubin occurs at 460 millimicra (fig. 4).

(3) *Methæmoglobin.*—Both the alkaline and natural forms of the oxidized hæmoglobin molecule differ from the oxygenated oxyhæmoglobin molecule in that the iron content of the molecule is in the ferric form. Their characteristic curves show a sharp fall to the first two absorption bands at 540 and 575 millimicra and another fall to 600 millimicra, after which there is a slight plateau with another fall at 630 millimicra. The absorption bands at 540 and 575 millimicra, in which the former is of greater density, are those of the alkaline form, while the band at 630 millimicra is due to the neutral form of methæmoglobin (fig. 5).

(4) *Pigment mixtures.*—In interpreting spectrophotometric records it is important to note that in pigment mixtures highly diluted by cerebrospinal fluid, sharp peaks of absorption will occur only for pigments having very narrow absorption bands. In pigment mixtures with a low concentration of bilirubin its broad

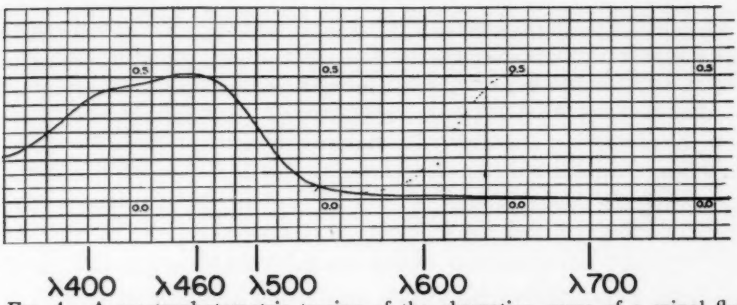

FIG. 4.—A spectrophotometric tracing of the absorption curve of a spinal fluid in a case of cerebral hæmorrhage of several weeks' duration. Each vertical line equals 13·5 millimicra. Maximum absorption occurs at 460 millimicra and is that absorption seen when bilirubin is present.

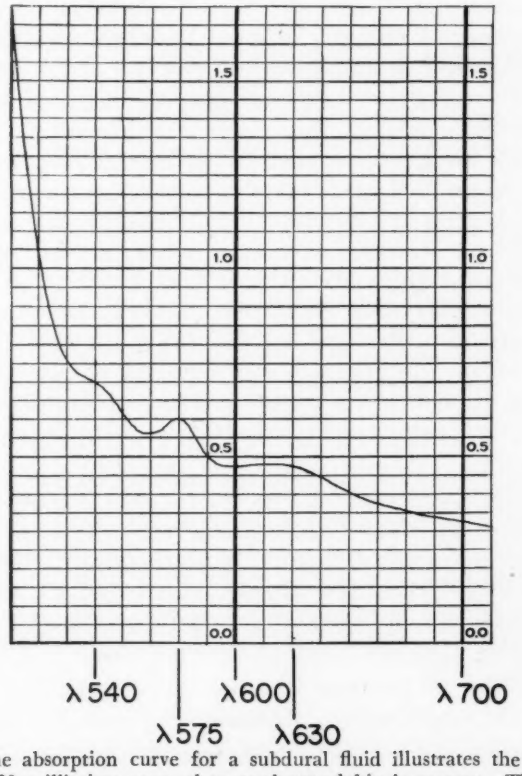

FIG. 5.—The absorption curve for a subdural fluid illustrates the plateaux at 540, 575 and 630 millimicra seen when methæmoglobin is present. The difference in density at 540 and 575 millimicra should be compared with the identical absorption density at these wave-lengths in oxyhæmoglobin absorption curves. Each vertical line equals 13·5 millimicra.

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absorption band appears as a plateau or slight elevation with maximal absorption at 460 millimicra superimposed upon the density curves produced by the additional pigments present. Oxyhæmoglobin with a very narrow absorption band at 575 millimicra even in very dilute solutions will be readily apparent in pigment mixtures.

After making the continuous absorption tracings the fluid was removed from the absorption chamber and analysed for total protein. In many of the fluids, the bilirubin concentration was obtained by a micro-analytical method for the determination of serum bilirubin. In addition, in 112 of the 176 fluids examined, the following tests were done:

(1) *The benzidine test.*—A saturated solution of benzidine in 3 per cent acetic acid was combined with equal amounts of hydrogen peroxide. The acid benzidine solution was added drop by drop to 2 c.c. of the supernatant cerebrospinal fluid. The presence of the iron-containing pigments oxyhæmoglobin and methæmoglobin was roughly estimated by the number of drops necessary to produce the blue discoloration. Dry chemically clean equipment was necessary to avoid hæmolysis and contamination. The use of Hemosol[R], a detergent which dissolves all blood pigment, has been useful in keeping glass equipment chemically clean and free of hæmoglobin derivatives.

(2) *van den Bergh test.*—A modification of the Malloy-Evelyn method for the determination of serum bilirubin suitable for micro-analytical use was devised (Barrows and Rourke). 1 ml. of cerebrospinal fluid was combined with 0·5 ml. of methyl alcohol and 0·5 ml. of diazo reagent. This fluid was compared with a blank consisting of 0·5 ml. of methyl alcohol, 1 ml. of cerebrospinal fluid and 0·5 ml. of dilute hydrochloric acid (1·5 ml. of concentrated hydrochloric acid plus 88·5 ml. of water). After standing for half an hour, the two fluids were compared. A visible colour change to the naked eye indicated a positive reaction. The colour change was graded from a slight decrease in colour recorded as 1+, to a pink 2+, and to a violet 3+.

(3) *Potassium cyanide test.*—A 0·1 per cent colourless potassium cyanide solution was added drop by drop to 2 ml. of the supernatant cerebrospinal fluid. A blank was prepared by adding the same number of drops of distilled water to another 2 ml. of the same cerebrospinal fluid. A positive result for methæmoglobin was interpreted as a rapid colour change to a cherry-red or orange-brown in comparison with the blank (Stadie, 1920).

Results

One hundred and forty-nine fluids from 68 patients were subdivided into four groups according to the nature of the pathological process: (1) Subarachnoid, ventricular or subdural hæmorrhage; (2) Spinal, sub-

arachnoid or ventricular block; (3) Liver disease with jaundice and (4) A miscellaneous group in which pathogenesis was unknown. In addition, there was an analysis of twenty-seven non-pigmented fluids from normal controls and from patients with "traumatic taps" (Table I).

TABLE I

	Classification	*No. of cases*	*No. of fluids*	*Pigment producing colour*
Group I	*Hæmorrhage*			
	Subarachnoid or ventricular	31	81	Oxyhæmoglobin and Bilirubin
	Subdural hæmatoma	8	8	Methæmoglobin
Group II	*Block*			
	Spinal, subarachnoid or ventricular	7	32	Bilirubin
Group III	*Liver disease with jaundice*	12	12	Bilirubin
Group IV	*Miscellaneous*			
	Subdural effusions	2	8	Bilirubin
	Cystic fluids	8	8	Bilirubin
Group V	*Non-pigmented fluids*			
	Controls	20	20	No pigment
	Traumatic tap	7	7	No pigment
	Total	95	176	

In Group I eighty-one xanthochromic fluids from 31 patients with hæmorrhage were available for study. Oxyhæmoglobin absorption curves were obtained from these fluids in the early stages of subarachnoid or cerebral hæmorrhage. Serial determinations in several cases traced the development of pigments in fluids following a hæmorrhage (Table II). Oxyhæmoglobin appeared in the centrifuged xanthochromic supernatant fluid within two hours of the onset of clinical symptoms of hæmorrhage. On the third or fourth day, a plateau in the oxyhæmoglobin curve at 460 millimicra indicated the appearance of bilirubin as an additional pigment. During the next week, the amount of bilirubin increased while the amount of oxyhæmoglobin decreased. In the second and third weeks, the bilirubin gradually disappeared providing that no further bleeding occurred. In one patient where there were 800,000 red blood cells per c.mm. in the spinal fluid six hours after the onset of hæmorrhage both oxyhæmoglobin and bilirubin were present. This was the only exception to the rule that oxyhæmoglobin is the only pigment in cerebrospinal fluid during the first hours after the occurrence of subarachnoid hæmorrhage. The pigmentation of the cerebrospinal fluid in this case was produced not only by the rapid hæmolysis of erythrocytes, liberating oxyhæmoglobin, but also by the introduction of serum bilirubin in measurable quantity from the blood. Case 6 in Table II illustrates the spinal fluid findings in a typical un-

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TABLE II.—TIME RELATIONSHIPS BETWEEN HÆMORRHAGE AND PIGMENTED FLUID

Fluid No.	*Duration after hæm.*	*Source of fluid*	*Supn't. colour*	*R.B.C./ c mm.*	*Tot. prot. mg./100 ml.*	*Tot. bil. mg./100 ml.*	*Pigment abs. curve*	*V.D.B.*	*C.S.F. Benz.*	*K.C.N.*
			Case No. 1—Cerebral hæmorrhage							
1	2 hours	L.P.	pink-yellow	27,400	—	—	Oxyhæmoglobin	—	—	—
			*Case No. 2—Subarachnoid hæmorrhage							
1	3 hours	"	chrome-yellow	1,120,000	—	—	Oxyhæmoglobin Bilirubin	—	—	—
			*Case No. 3—Cerebral hæmorrhage							
1	6 hours	"	yellow	800,000	2,400	0·26	Oxyhæmoglobin Bilirubin	+++	1+	0
			Case No. 4—Subarachnoid hæmorrhage							
1	4 hours	"	light yellow	71,000	256	—	Oxyhæmoglobin	—	—	—
2	3 days	"	bright yellow	51,000	224	—	Bilirubin	—	—	—
			Case No. 5—Post-operative bleeding							
1	6 hours	"	faint buff	1,810	65	—	Oxyhæmoglobin	—	—	—
			*Case No. 6—Subarachnoid hæmorrhage							
1	4 hours	"	pink-yellow	450,000	—	—	Oxyhæmoglobin	—	—	—
2	24 hours	"	light yellow	700,000	—	—	Bilirubin Oxyhæmoglobin	—	—	—
3	4 days	"	bright yellow	390,000	74	—	Bilirubin Oxyhæmoglobin	—	—	—
4	7 days	"	bright yellow	6,450	72	—	Bilirubin	—	—	—
5	15 days	"	light yellow	420	148	—	Bilirubin	—	—	—
6	18 days	"	light yellow	10	—	—	Bilirubin	—	—	—
			*Case No. 7— Cerebral hæmorrhage							
1	4 days	"	orange	19,000	250	0·97	Bilirubin Oxyhæmoglobin	—	—	—
2	8 days	"	golden	400	245	0·47	Bilirubin Oxyhæmoglobin	—	—	—
3	12 days	"	light yellow	400	95	0·17	Bilirubin Oxyhæmoglobin	—	—	—

4	15 days	L.P.	light yellow	100	80	0·05	Bilirubin Oxyhæmoglobin	—	—	—
5	22 days	"	faint yellow	60	—	—	Bilirubin Oxyhæmoglobin	—	—	—
6	30 days	"	faint yellow	0	—	—	Bilirubin	—	—	—
			*Case No. 8—Meningocerebral hæmorrhage							
1	11 days	"	deep yellow	170	—	—	Bilirubin (trace oxyhgb.)	+++	1+	0
2	15 days	"	orange-yellow	5,670	—	—	Bilirubin Oxyhæmoglobin	+++	1+	0
3	27 days	"	orange	6,520	—	—	Oxyhæmoglobin Bilirubin	+++	1+	0
4	46 days	"	yellow	800	—	—	Bilirubin Oxyhæmoglobin	+++	4+	0
5	48 days	Vent	cherry-red	750,000	—	—	Oxyhæmoglobin	0	1+	0
6	50 days	"	rusty-red	250,000	—	—	Methæmoglobin (oxyhgp.)	0	1+	+++
7	55 days	"	rusty-red	25,000	—	—	Methæmoglobin (oxyhgp.)	0	1+	+++
8	55 days	L.P.	yellow	100	—	—	Bilirubin	+++	25+	0
			*Case No. 9—Meningocerebral hæmorrhage							
1	3 days	"	yellow-orange	52,000	—	—	Oxyhæmoglobin (bilirubin)	+++	1+	0
2	12 days	"	rusty-red	290	240	—	Methæmoglobin (bilirubin)	0	1+	0
3	18 days	"	yellow	15	72	—	Bilirubin	+++	15+	0

NOTE.—The numerals in the column for the benzidine reaction of C.S.F. indicate the number of drops required to give a positive reaction.

* Diagnosis proved by autopsy.

complicated subarachnoid hæmorrhage. As the red blood cell count in the spinal fluid gradually decreased, the oxyhæmoglobin liberated at the onset of hæmorrhage was broken down to bilirubin. Case 8 in Table II illustrates the varying spinal fluid picture that may occur in an aneurysm with recurrent bleeding. The first cerebrospinal fluid examination on the eleventh day showed a small amount of oxyhæmoglobin and the presence of bilirubin. On the fifteenth day both oxyhæmoglobin and bilirubin were present. On the forty-sixth day the predominant pigment was bilirubin but two days later the clinical signs and symptoms indicated another episode of bleeding. The red coloration of the supernatant fluid as well as the red blood cell count confirmed this. Spectrophotometric determinations showed pure oxyhæmoglobin. Ventricular drainage instituted during the final week of the patient's illness showed a rusty-red supernatant fluid comprised of both oxyhæmoglobin and methæmoglobin. The constant drainage with rapid removal of fluid from the ventricle must have prevented the formation of bilirubin. In contrast the lumbar spinal fluid was deep yellow owing to its high content of bilirubin, the only pigment detected. At autopsy there was a partial block of the fourth ventricle with compression of the cerebellar tonsils upon lower medulla and spinal cord.

The subdural fluids from 8 patients with subacute or chronic subdural hæmatomata were studied. Nine days was the shortest interval between the time of trauma and removal of subdural fluid at operation. The alkaline and neutral forms of methæmoglobin were found in every case. In addition, bilirubin was also present in six of the subdural fluids (Table III). In none of these cases did either form of methæmoglobin appear in the lumbar spinal fluids. The yellow colour of cerebrospinal fluid in chronic subdural hæmatomata has been due to bilirubin in the few random observations that have been made. Having the same absorption maxima as the alkaline form of methæmoglobin at 540 and 575 millimicra, it was not possible to exclude the presence of oxyhæmoglobin. The difference in density at these two wave-lengths, however, suggested methæmoglobin as the pigment primarily responsible for coloration rather than oxyhæmoglobin, where absorption maxima at 540 and 575 millimicra is of the same density.

In an intracerebral hæmorrhage in which rusty-red ventricular fluid showed the absorption bands of methæmoglobin (neutral at 630 millimicra) and oxyhæmoglobin, the spinal fluid was yellow and showed an absorption curve of bilirubin. In an additional case, an intracerebral hæmatoma was evacuated and analysis revealed methæmoglobin (neutral at 630 millimicra) and oxyhæmoglobin from the hæmatoma while the ventricular

TABLE III.—SUBDURAL HÆMATOMA

Estimated

TABLE III.—SUBDURAL HÆMATOMA

Fluid No.	Colour	Estimated duration of subdural	T.P. mg./100 ml.	pH	Spectr. curve	Subdural Fluid V.D.B.	Benz.	K.C.N.
1	Brown	2 weeks	2,100	7·0	Methgb. Bilirubin	−	+	+
2	Brown-black	3 weeks	n.d.	8·0	Methgb. Bilirubin	−	+	+
3	Reddish-brown	3 months	n.d.	n.d.	Methgb. Bilirubin	n.d.	n.d.	n.d.
4	Reddish-brown	12 days	n.d.	n.d.	Methgb. Bilirubin	”	”	”
5	Reddish-brown	—	2,000	n.d.	Methgb.	”	”	”
6	Olive	9 days	2,000	n.d.	Bilirubin Methgb.	”	”	”
7	Reddish-brown	—	5,400	8·0	Bilirubin Methgb.	+	+	+
8	Brown-black	2 weeks	3,000	8·5	Methgb.	−	+	+

TABLE IV.—SPINAL, SUBARACHNOID OR VENTRICULAR BLOCK

Diagnosis	Colour	Total protein mg./100 ml.	Total bil. mg./100 ml.	Direct bil. mg./100ml.	Pigment curve	R.B.C.	C.S.F. V.D.B.	Benz.	K.C.N.
Cord tumour*	Yellow	2,000	0·4	—	Bilirubin (trace oxy.)	851	—	—	—
Cord tumour	Light yellow	300	—	—	Bilirubin (460λ)	—	+	0	0
Obstructive hydrocephalus	Yellow	2,900	0·61	—	Bilirubin (460λ)	5	+++	0	0
	Yellow	2,900	0·61	—	”	2	+++	0	0
	Yellow	2,400	1·20	0·9	”	8	+++	0	0
	Yellow	2,100	0·33	—	”	4	+++	0	0
	Yellow	1,800	0·40	—	”	4	+++	0	0
	Yellow	1,800	0·20	—	”	10	+++	0	0
	Yellow	1,600	1·10	0·2	”	5	+++	0	0
	Yellow	2,800	0·52	0·42	”	3	+++	0	0
	Yellow	2,800	0·27	0·27	”	8	+++	0	0
	Yellow	2,350	0·45	0·22	”	0	+++	0	0
Obstructive hydrocephalus*	Yellow	520	0·28	—	Bilirubin (460λ)	400	—	—	—
Obstructive hydrocephalus*	Light yellow	132	0·20	—	Bilirubin (trace oxy.)	380	—	—	—
Cord tumour	Light yellow	353	0·09	—	Bilirubin (trace oxy.)	1,800	—	—	—
Meningomyelitis* with hæm. exudate	Brown	4,100	—	—	Methæmoglobin (bilirubin)	10	—	—	—

* Diagnosis proved by autopsy.

and spinal fluids showed oxyhæmoglobin and bilirubin. Another patient with a traumatic intracerebral hæmatoma had a blackish-brown ventricular fluid which showed absorption curves of a mixture of methæmoglobin (neutral at 630 millimicra) and bilirubin. Only bilirubin was present in the lumbar spinal fluid. A rusty-red supernatant spinal fluid was found on the twelfth day in a patient with a meningocerebral hæmorrhage. Methæmoglobin (neutral at 630 millimicra) and bilirubin were the pigments detected. After two and a half weeks only bilirubin was responsible for the xanthochromic fluid.

In Group II in the fluids from 7 cases of the spinal, subarachnoid or ventricular blocks, the yellow coloration was always associated with a high protein content. The pigment responsible for xanthochromia in three of the seven fluids was bilirubin with maximal absorption at 460 millimicra while in three cases (two cord tumours and one obstructive hydrocephalus) there was a pigment mixture of bilirubin and a very small amount of oxyhæmoglobin. Quantitative tests of bilirubin gave values from 0·09 mg. per 100 ml. to 1·2 mg. per 100 ml. in 5 of the 7 cases. In the seventh case, the block to spinal fluid was caused by a syphilitic meningomyelitis. In addition, at autopsy, the chronic inflammatory exudate contained considerable amounts of blood, the source of which was never adequately explained. In this patient, the spinal fluid below the obstruction was coffee coloured with a protein of 4,100 mg. per 100 ml. and spectroscopic evidence of methæmoglobin and bilirubin (Table IV). In the patient with the obstructive hydrocephalus (Case 3 in Table IV) the total protein was 2,350 mg. per 100 ml. with 2,050 mg. per 100 ml. of albumin and 300 mg. per 100 ml. globulin. The total bilirubin of this fluid was 0·45 mg. per 100 ml. and the direct bilirubin was 0·22 mg. per 100 ml.

In Group III, which was composed of cerebrospinal fluid from 12 jaundiced patients with severe liver disease, 10 showed the absorption curves for bilirubin at wave-lengths between 430 and 460 millimicra (Table V). In three of the fluids in this group there was maximal absorption at 460 millimicra although the protein was not elevated. In 2 patients who gave a history of jaundice of about two weeks' duration, the serum bilirubin values were 20·2 mg. per 100 ml. to 35·4 mg. per 100 ml. and the spinal fluids had a greenish-yellow discoloration. The bilirubin content was 0·1 mg. per 100 ml. and 0·24 mg. per 100 ml. respectively.

In the miscellaneous group, 2 cases of subdural effusion secondary to meningitis produced curves characteristic of bilirubin with absorption maximal at 460 millimicra. By chemical analysis, bilirubin ranging in amounts from 0·8 mg. per 100 ml. to 1·25 mg. per 100 ml. was found. All of these subdural fluids had an elevated total protein (Table VI). High

TABLE V.—LIVER DISEASE WITH JAUNDICE

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Fluid No.	Diagnosis	Duration jaundice	Colour C.S.F.	T.P. mg./100 ml. C.S.F.	Tot. bil. mg./100 ml. C.S.F.	Serum bil. mg./100 ml.	Spect. absorp. curve	Wave-length	C.S.F. R.B.C.	C.S.F. V.D.B.	C.S.F. Benz.	C.S.F. K.C.N.
1	Cirrhosis*	1 week	Clear	35	0·0	3·0	none	none	0	—	—	—
2	Cirrhosis*	7 days	Clear	40	0·0	8·0	none	none	0	—	—	—
3	Cirrhosis*	10 days±	Green-Yellow	40	0·1	20·2	Bilirubin	460	3	+	—	—
4	Cirrhosis	2-3 weeks	Green-Yellow	61	0·24	35·4	"	460	8	+	—	—
5	Cirrhosis	3 weeks+	"	40	0·08	17·0	"	460	0	+	—	—
6	Cirrhosis	28 days±	"	34	0·15	12·8	"	440	0	+	—	—
7	Cirrhosis	30 days	"†	34	0·20	21·8	"	438	4	+	n.d.	
8	Cirrhosis	32 days	"	38	0·02	8·9	"	430	84	+	"	
9	Cirrhosis	36 days	"	15	0·10	6·3	"	430	0	+	"	
10	Cirrhosis	40 days	"	20	0·70	19·6	"	425	0	+	"	
11	Ca. gall bl.	28 days	"	50	0·15	13·2	"	440	0	+	"	
12	Ca. pancreas	24 days	"	72	0·20	19·0	"	430	0	+	"	

*Diagnosis proved by autopsy.

†An aliquot sample of this fluid retained its colour and had an identical spectral absorption curve after being kept in the dark for one week; a similar sample of the same fluid lost its colour and had a non-specific curve after being exposed to daylight for one week.

TABLE VI.—SUBDURAL EFFUSION FLUIDS

Source of fluid	Duration of effusion	Colour	R.B.C./ c.mm.	Tot. prot. mg./100 ml.	Tot. bil. mg./100 ml.	Pigment abs. curve
CASE NO. 1						
Right subdural tap	14 days	Dark yellow	15,000	710	0·62	Bilirubin
Right subdural tap	15 days	Yellow	—	630	—	Bilirubin
Left subdural tap	16 days	Light yellow	—	705	—	Bilirubin
Operation—right side	21 days	Yellow	All enmeshed in pellicle	600	—	Bilirubin (trace oxyhæmoglobin)
CASE NO. 2						
Right subdural tap	9 days	Dark yellow	—	1,480	1·0	Bilirubin
Left subdural tap	10 days	Dark yellow	—	1,480	0·8	Bilirubin
Right subdural tap	12 days	Yellow	—	580	1·0	Bilirubin
Left subdural tap	12 days	Yellow	—	560	1·25	Bilirubin

TABLE VII.—CYSTIC FLUIDS

Fluid No.	*Diagnosis*	*Colour fluid*	*Pigment abs. curve*	*T.P. mg./100 ml.*	*Tot. bil. mg./100ml.*	*V.D.B.*	*K.C.N.*	*Benz.*	*R.B.C.*
1	Porencephalic cyst	Yellow	Bilirubin	2,400	0·22	+++	Neg.	Neg.	50
2	Glioblastoma cyst	Yellow	Bilirubin (oxyhæmoglobin)	2,000	—	—	Neg.	+++	—
3	Glioblastoma cyst	Yellow	Bilirubin	5,100	1·88	—	—	—	2,300
4	Glioblastoma cyst	Dark amber	Bilirubin (trace oxyhgb.)	3,500	0·33	—	—	—	—
5	Craniopharyngioma cyst	Amber	Bilirubin (trace oxyhgb.)	3,500	1·24	—	—	—	112
6	Craniopharyngioma cyst	Dark yellow	Bilirubin Oxyhæmoglobin	2,700	0·5	—	—	—	800
7	Craniopharyngioma cyst	Yellow	Bilirubin (oxyhæmoglobin)	—	—	+++	Neg.	—	3,600
8	Craniopharyngioma cyst	Brown	Methæmoglobin Bilirubin (oxyhæmoglobin)	—	—	Neg.	+++	+++	—

TABLE VIII.—NORMAL FLUIDS AND TRAUMATIC TAPS

Fluid No.	*Type of puncture*	*Supernatant C.S.F.*	*R.B.C/ c.mm.*	*Benz.*	*V.D.B.*	*K.C.N.*	*Spectro. curve (Supernatant C.S.F. for all tests)*
1–20	Uncomplicated	Clear—colourless	8-10 aver.	—	—	—	No absorption
21	Traumatic tap	"	17,280	Neg.	Neg.	Neg.	" "
22	"	"	1,746	"	"	"	" "
23	"	"	225	"	"	"	" "
24	"	"	117	"	"	"	" "
25	"	"	1,026	"	"	"	" "
26	"	"	11,808	"	"	"	" "
27	"	"	5,200	"	"	"	" "

TABLE IX.—EXPERIMENTAL STUDY OF BLOOD IN SPINAL FLUID

Fluid No.	*Duration of R.B.C. in C.S.F.*	*Wave-length absorption*	*Density*	*Pigment curve*
1	1 hour	412	2·0	Oxyhæmoglobin
		540	0·5	
		575	0·5	
2	9 hours	412	2·0	Oxyhæmoglobin
		540	0·35	
		575	0·35	
3	30 hours	415	3·5	Oxyhæmoglobin
		490	1·05	Methæmoglobin
		540	1·07	
		575	0·85	
		630	0·5	
4	48 hours	412	2·8	Methæmoglobin
		540	1·24	
		575	1·16	
		630	0·45	
5	96 hours	490	0·65	Methæmoglobin
		540	0·8	
		575	0·67	
		630	0·25	
6	6 days dil. 1 : 2	490	1·68 × 3	Methæmoglobin
		540	1·8 × 3	
		575	1·5 × 3	
		630	0·67 × 3	
7	23 days dil. 1 : 3	490	1·07 × 4	Methæmoglobin
		540	1·17 × 4	
		575	0·97 × 4	
		630	0·35 × 4	

protein fluids from seven cysts associated with brain tumour showed curves of bilirubin with absorption at 460 millimicra. Chemical determinations of two of these cyst fluids gave bilirubin values of 1·24 mg. per 100 ml. and 1·88 mg. per 100 ml. Methæmoglobin was found in 1 of the 4 cases of cystic craniopharyngioma. A porencephalic cyst contained fluid with a total protein of 2,400 mg. per 100 ml. and showed a bilirubin value of 0·22 mg. per 100 ml. (Table VII).

In Group V, which consisted of twenty non-pigmented spinal fluids none showed an absorption curve in the visible spectrum. The centrifugal supernatant fluids from 7 patients with traumatic taps also had no absorption curve in the visible spectrum nor was any pigment detected by the naked eye (Table VIII).

In view of the findings of several pigments being responsible for the appearance of xanthochromic fluids, the question arose as to their relationship and the nature of their transformation from one form to another. In the uncomplicated subarachnoid hæmorrhage *in vivo* where there has not been tissue destruction by intracerebral extension, oxyhæmo-

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globin is gradually broken down to bilirubin with no intermediary step. An experimental study of the fate of blood in the cerebrospinal fluid was carried out *in vitro*. Seven samples of sterile lumbar spinal fluid each measuring approximately 4·5 ml. were collected during a pneumo-encephalogram in a patient with cortical atrophy. At the same time blood was obtained from the antecubital vein and approximately 0·1 ml. was delivered into the samples of spinal fluid. The transfer was made under sterile conditions and the fluids were agitated gently. All fluids were incubated at 37°C. until examined. There were approximately 87,500 red blood cells per c.mm. in each tube initially. Spectrophotometric absorption curves of the samples were obtained at varying intervals, one sample being used for each determination. Oxyhæmoglobin was found in the initial sample. Between the ninth hour and the thirtieth hour specimens, mathæmoglobin appeared and persisted for at least twenty-six days. Bilirubin was never detected by spectrophotometric analysis (Table IX). Cultures taken at the time of spectrophotometric analysis were negative. In this attempt, therefore, to reproduce subarachnoid hæmorrhage *in vitro,* methæmoglobin appeared as an intermediary product after the breakdown of oxyhæmoglobin in normal spinal fluid.

Discussion

Oxyhæmoglobin, bilirubin and methæmoglobin are the pigments which commonly occur in coloured cerebrospinal fluid. In the pure form each has a characteristic colour. Oxyhæmoglobin is red but with dilution varies from orange to an orange-yellow. Methæmoglobin is brown and bilirubin is a canary yellow. Mixtures of these three pigments produce various combinations of these colours.

During the process of hæmolysis in the subarachnoid space, oxyhæmoglobin is the first pigment to appear. In spinal fluid examined two hours following the clinical onset of hæmorrhage, oxyhæmoglobin was visible in the supernatant fluid and detected by the spectrophotometer. This pigment rapidly increases in amount to become maximal in the first few days and if no further bleeding occurs, gradually diminishes over a seven to nine day period. Bilirubin, the iron-free pigment derivative of the hæmoglobin molecule, appears usually in two to three days and increases in amount as oxyhæmoglobin decreases. The amount of bilirubin formed is closely related to the number of erythrocytes hæmolysed and to the amount of oxyhæmoglobin formed. The duration of detectable bilirubin in the cerebrospinal fluid depends upon the concentration of the bilirubin. It may persist for two to three weeks. Following a subarachnoid hæmorrhage, when bilirubin has been separated from the hæm portion of the

hæmoglobin molecule, it is conceivable that the iron pigment is taken up by the cells of the meninges.

Methæmoglobin, the ferric form of hæmoglobin, will form spontaneously at a slow rate from reduced hæmoglobin in a test tube, but we have not succeeded in converting hæm compounds to bilirubin *in vitro* by the incubation of red blood cells with normal sterile cerebrospinal fluid over a twenty-six day period. Oxyhæmoglobin was present in the first specimen. Methæmoglobin was present between the six-hour and the thirty-hour specimens and persisted for twenty-six days. The conversion of reduced hæmoglobin to methæmoglobin is possible both *in vitro* and *in vivo*. It is apparent that the conversion of hæm compounds to bile pigments requires specific conditions of temperature, concentration and pH and the presence of both oxygen and an appropriate reducing system. These conditions are present only in living cells. From our observations, it appears that methæmoglobin ordinarily is not an intermediary product in the transformation of oxyhæmoglobin to bilirubin in the subarachnoid space. The absorption bands of neither of these pigments obscure the neutral band of methæmoglobin, and when methæmoglobin does appear it is under a special set of conditions in which red blood cells undergo degradation in an enclosed space such as in subdural hæmatoma, loculated spinal fluid or cyst fluid or intracerebral hæmatoma.

Methæmoglobin was found in the spinal fluids of 2 patients. One had a syphilitic meningomyelitis, complete block and a hæmorrhagic chronic exudate. The other had a meningocerebral hæmorrhage. Methæmoglobin was detected in the ventricular fluid in a patient with an intracerebral hæmatoma. It was the predominant pigment in the eight subdural hæmatomas and in six of these fluids bilirubin was also present. While the earliest opportunity to obtain subdural fluid *in vivo* was at an operation one week following the history of trauma, it is probable that this pigment forms within a few hours or days. At least one can say that experimentally *in vitro* a pigment was produced which gave the spectral characteristics of methæmoglobin thirty hours after incubation of approximately 100,000 red blood cells in sterile spinal fluid at 37°C. The common feature noted in all cases in which methæmoglobin was formed was encapsulation of a mass of extravasated blood. It is possible that this encapsulation impedes the efficiency of the oxidative-reduction process necessary for the conversion of reduced hæmoglobin to bilirubin.

In all of the 7 cases in which there was an obstruction to the flow of cerebrospinal fluid, the protein was markedly elevated and bilirubin was the predominant pigment. Similarly bilirubin was the predominant pigment in the fluids from cases of subdural effusion secondary to menin-

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gitis and in the fluids contained in cysts within the substance of the brain. A small amount of oxyhæmoglobin was also present in fluids from four of the cysts. In hæmorrhagic fluids from an encapsulated space the derivative of oxyhæmoglobin is usually methæmoglobin and not bilirubin. This would be additional evidence to suggest that the bilirubin in most cystic fluids is a result of a transudate from blood plasma and not a breakdown product of blood pigment. The common factor in the fluids from the cysts, subdural effusions and loculated fluid within the ventricles of subarachnoid space is the elevation of the total protein. Nevertheless, our data offer no conclusive proof that bilirubin is bound to protein in a bilirubin-protein complex. In cerebrospinal fluid with a normal protein, the bilirubin concentration is too small to be visible but as the total protein is elevated over approximately 100 mg. per 100 ml. bilirubin concentration is present in quantities visible to the naked eye.

The pathogenesis of subdural effusion in infants secondary to a meningitis is imperfectly understood. In both of our cases the absorption curve of subdural fluid from the initial tap was characteristic of bilirubin with no evidence of oxyhæmoglobin or methæmoglobin. The duration of the effusion from one to two weeks and the absence of oxyhæmoglobin or methæmoglobin in the initial tap would indicate that the xanthochromic colour is due to increased total protein and the bilirubin bound to the protein-complex rather than to hæmorrhage.

In the group of jaundiced patients, bilirubin was the only pigment detected. The level of elevation of serum bilirubin and the duration of jaundice appear to be important factors in production of this pigmented spinal fluid. There was no relationship between the level of bilirubin in the cerebrospinal fluid and the level of spinal fluid protein in this group. One may conclude that the xanthochromia is a result of a diffusion of pigment into the cerebrospinal fluid and is not a transudate of protein-bound bilirubin.

The simple biochemical tests confirmed most of the spectrophotometric data. The benzidine reaction was positive whenever the absorption spectrum of oxyhæmoglobin was obtained. There were no false positives. This test was negative in all cases of "traumatic tap" providing the fluid was analysed at the time of the trauma. The modification of the van den Bergh test was positive when bilirubin was identified by the spectrophotometer even in amounts as small as 0·08 mg. per 100 ml. except when the presence of the brown pigmentation of methæmoglobin or the red of pure oxyhæmoglobin masked the colour reaction. When the brown pigment of methæmoglobin was readily visible, the potassium cyanide

test was positive but for smaller amounts, the colour change to the red cyanohæmoglobin was not apparent.

In the course of this study we were impressed with the sensitivity of the normal human retina in recognizing the colour changes in spinal fluids. It is of practical importance, therefore, in the examination of cerebrospinal fluid to compare the specimen by naked eye with clear tap water in tubes of exactly the same size and against a white background. Any change in colour of the supernatant is highly suspicious of a pathological lesion in the nervous system. Prompt centrifugation of the bloody fluid and rapid separation of the supernatant will help to differentiate a traumatic tap from a pathological fluid. Blood serum diluted 200 times is colourless so that supernatant fluid from cerebrospinal fluid with 25,000 red blood cells per c.mm. would also be colourless unless a pathological process had occurred prior to the puncture.

Xanthochromia, as the term is applied to cerebrospinal fluid, may include a variety of colours. It is important to describe the colour of the fluid accurately and to follow the cell counts carefully. In addition to this method of inspection, the simple confirmatory tests and if available, the spectrophotometer, may enable one to diagnose and interpret the clinical course of the neurological disease responsible for the discoloration of the cerebrospinal fluid.

Conclusions

(1) Oxyhæmoglobin, bilirubin and methæmoglobin are the pigments which commonly occur in coloured cerebrospinal fluid.

(2) Oxyhæmoglobin appears at the onset of hæmorrhage, progresses to a maximum the first few days and then gradually diminishes in amount. Bilirubin appears in two to three days and increases in amount as oxyhæmoglobin decreases. Bilirubin persists for two to three weeks. Experiment *in vitro* suggested that only the action of living cells can produce bilirubin.

(3) Methæmoglobin is found in fluids from subdural and intracerebral hæmatomas, craniopharyngiomas, and in fluids near encapsulated blood.

(4) In cases in which there was obstruction to the flow of cerebrospinal fluid, cystic fluids and subdural effusions, the protein was elevated and bilirubin was the predominant pigment. The transudation of bilirubin complex from blood plasma is suggested in such situations.

(5) In 10 of the 12 jaundiced patients, the spinal fluid was xanthochromic and bilirubin was the only pigment detected.

(6) The benzidine, van den Bergh and potassium cyanide tests are useful simple confirmatory tests that can be performed in any ward laboratory when spectrophotometric methods are not available.

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PROCAINE AMIDE IN THE TREATMENT OF MYOTONIA

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INTRODUCTION

CERTAIN disorders of muscle, the myotonias, are characterized by delayed relaxation after strong contraction. In many cases the disability is trifling but in others it may be severe and even be associated with pain. Any alleviation is therefore welcomed by patients, and more especially by those in whom slow relaxation is dangerous because of occupational risks.

Until the advent of modern techniques of investigation it was assumed that the slow relaxation of the myotonic muscle after a strong contraction was due to predominance of "slow" over "fast" fibres in the muscles of these patients (Bing and Haymaker, 1939). Electromyographic investigation has, however, revealed that the after-contraction is associated with fast repetitive action potentials in the affected muscle fibres (Brown and Harvey, 1939; Denny-Brown and Foley, 1949; Landau, 1952). These repetitive action potentials follow strong voluntary contraction of the muscle, or mechanical or electrical stimulation. They are evidence that the after-contraction has the nature of a tetanus rather than a slow twitch and, since there is repetitive excitation of random single fibres, that the phenomenon is myogenic. Consequently a drug preventing neuromuscular transmission can only achieve control of the myotonic state at the expense of reducing voluntary innervation of the muscle. A substance is required which will stabilize the polarized membrane of the muscle fibre so that repetitive firing will not occur following normal innervation.

Various preparations of quinine have been used with success (Wolf, 1936) but unfortunately the required therapeutic effect is rarely obtained without mild symptoms of quinine poisoning so that many patients prefer to suffer the inconveniences of the myotonia. The "quinine-like" action of procaine amide on repetitive firing of cardiac muscle suggested that it might be equally effective in the control of myotonia. As the effects of

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procaine amide on skeletal muscle have not hitherto been reported, limited studies were made to establish the nature of its action by comparison with that of drugs known to block neuromuscular transmission.

(1) Pharmacological Studies

Material and Methods

The effect of intravenously injected procaine amide was compared, in 2 patients with dystrophia myotonica, with those of d-tubocurarine and decamethonium, given on different days under comparable conditions. Procaine amide was injected slowly (100 mg. per minute) while the patient was lying flat, the pulse-rate and blood pressure being recorded every two minutes. One patient was given 1,000 mg. and the other 800 mg. of the drug. The doses of d-tubocurarine and decamethonium were 10 mg. and 1·5 mg. respectively. The following observations were made before the injections and at intervals of five minutes thereafter. All examinations were made in the same room which has an approximately constant temperature and at the same time of day.

(*a*) *Active myotonia.*—With the wrist firmly fixed to prevent flexion, the patient gripped two of the examiner's fingers tightly for three seconds then attempted to open his hand fully and as quickly as possible. The time required to do this was estimated.

The duration of after-contraction of the flexor digitorum sublimis was recorded with an electromyograph (EMG) using surface electrodes (two Ag-AgCl discs of 1 cm. diameter placed 2 cm. apart) to avoid mechanical stimulation. Records were made of isometric and isotonic contraction of that muscle. Isometric contraction was tested by asking the patient to squeeze a 2 in. diameter baton as firmly as possible during a count of five seconds and then to relax immediately without opening the grip. The wrist was fixed as before. Isotonic contraction was recorded with the forearm strapped in an ergograph which was so designed that a weight was lifted when the fingers were flexed. The muscle then remained loaded while the pull was continued. When slight extension of the fingers occurred a spring-loaded brake prevented the weight from falling but allowed the fingers to extend without load. The cord attached to the fingers rotated a potentiometer so that finger movements could be recorded rather than the movements of the weight-pan as in conventional ergographs in which the fingers are passively extended by the full load. Three isotonic contractions of three seconds' duration were recorded at intervals of about one minute, followed by a series of contractions at maximum speed. The load used was just less than the greatest weight that the individual patient could lift and varied from 4 to 14 lb.

(*b*) *Percussion myotonia.*—The thenar, extensor digitorum, and deltoid muscles were struck sharply with a small reflex hammer. The tongue was struck via a spatula placed on edge. The slowly relaxing muscle contraction and the dimple caused by the blow were observed. No accurate measurements could be made.

(*c*) *"Needle" myotonia.*—This term is used to denote the repetitive action potentials induced in the relaxed muscle by movement in it of a needle electrode. The action potentials were observed on a cathode ray oscilloscope and a loud-speaker, using a conventional electromyograph with photographic recording. A time-scale was recorded on a second beam of the oscilloscope as was the ergograph described above. The usual coaxial needle electrodes were used.

(*d*) *Neuromuscular transmission.*—This was investigated by the technique described by Harvey and Masland (1941). The ulnar nerve at the elbow was stimulated supramaximally with thyratron-triggered condenser shocks at the rate of 10 per second. The integrated action potential of the hypothenar muscles was recorded by the surface electrodes already described. Grip strength was judged by means of the ergograph.

Results

So long as voluntary contraction was possible, myotonic after-contraction persisted after injection of d-tubocurarine or decamethonium. Percussion and "needle" myotonia were unchanged even when there was sufficient block of neuromuscular transmission to reduce the action potential of the supramaximally stimulated hypothenar muscles to 10 per cent–20 per cent of its previous size, with corresponding diminution of grip strength. In both patients, however, 800 mg. of procaine amide abolished the delayed relaxation of the flexor digitorum sublimis after maximal isometric or isotonic contraction and the rate of extension of the fingers after isotonic grip returned to normal. This was accompanied by abolition of the after-discharge in the EMG (Plate VI, fig. 1). Percussion myotonia appeared to be unchanged, but it is difficult to obtain valid comparisons of this test. On insertion of a needle electrode typical showers of myotonic potentials could still be induced but less readily than before and they repeated at lower frequencies (so that it was difficult to produce the typical high-pitched musical note in the loud-speaker). Muscle power, measured with the ergograph, was not appreciably affected. Sometimes it seemed to improve because of the relief from stiffness. There was no evidence of neuromuscular block.

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Discussion

Brown and Harvey (1939) noted that the after-contraction of the muscles of myotonic goats persisted after curarization (by close arterial injection) and even after degeneration of the motor nerve, suggesting that the myotonic action potentials originated in the muscle fibre. The extension of this finding to decamethonium block is of interest as the latter drug depolarizes the end-plate and the immediately adjacent membrane of the muscle fibre (Burns and Paton, 1951). It thus seems unlikely that the repetitive firing originates in the end-plate region exclusively. In our opinion lowered threshold and defective accommodation of the muscle fibre membrane are responsible. It is not our purpose to argue this thesis in this place but it has been stated as it provided the theoretical background for the present work. Substances known to have a stabilizing action on the membrane of excitable cells might be expected to have some therapeutic value in the control of myotonia. A drug of the procaine group suggested itself.

Though earlier workers (quoted by Harvey, 1939) attributed a curare-like action to procaine, later work (reviewed by Hunt and Kuffler, 1950) is more consistent with the idea that procaine has an ill-defined "stabilizing" or "freezing" action on the membrane of muscle and nerve. It is not denied that in high concentration a neuromuscular block may be produced but these concentrations are not reached *in vivo* (Ellis *et al.*, 1953). Hunt and Kuffler (1950) state that quinine has similar properties. The use of procaine hydrochloride and procaine amide in the control of certain ectopic arrhythmias of heart muscle offered support for the theory since

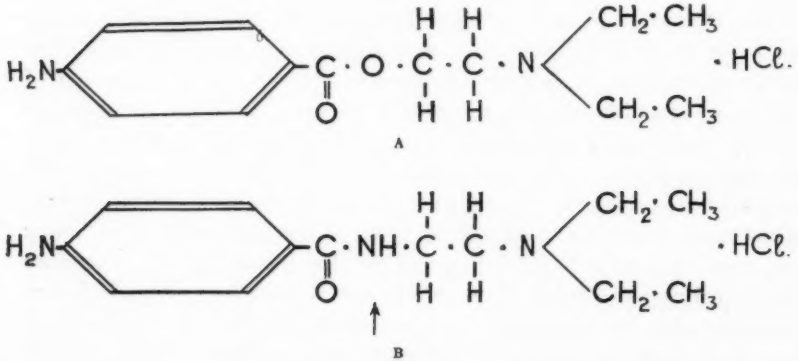

FIG. 2.—A, Procaine hydrochloride. B, Procaine amide.

there is evidence that ectopic systoles are due to repetitive firing of hyper-excitable foci in the cardiac syncytium (Scherf and Schott, 1953). Procaine amide is particularly effective in controlling repetitive firing of ventricular muscle, which receives no cholinergic nerve fibres (Nonidez, 1939), so that there is no question that the action is directly on the heart muscle.

Procaine amide was selected for clinical trial. It is widely and safely used in cardiological practice and can be taken orally. Its formula—p-amino-N-(2-dimethylaminoethyl) benzamide hydrochloride—differs from that of procaine hydrochloride by the substitution of an amide group for the ester group (fig. 2). Its special value is that it is less rapidly hydrolysed than procaine hydrochloride in the blood. Mark *et al.* (1951) found that plasma levels declined slowly after intravenous injection (ten–twenty per cent per hour). On oral dosage the plasma level reached maximum in about one hour. Absorption was relatively complete and 50–60 per cent was excreted unchanged in the urine. From 2–10 per cent was excreted as p-aminobenzoic acid or its conjugates. If the dose was repeated four times daily a plateau concentration was reached in the plasma in thirty-six to forty-eight hours and thereafter no further accumulation occurred. The drug concentration was higher in the tissues than in the plasma. These findings suggest that procaine amide should be equally effective when taken by mouth. Though it is safe to give the drug by injection if given slowly (100 mg. per minute) in doses of 500–1,000 mg., there is the possibility of causing postural hypotension and too rapid injection may cause cerebral stimulation (Mark *et al.*, 1951). These risks are absent when the oral route is used.

(2) Clinical Trial

Materials

Procaine amide was given by mouth to 9 patients with different types of myotonia (Table I). All patients had classical dysotrophia myotonica except Patients 8 and 9. Patient 8 was a powerfully built man with no muscle-wasting or testicular atrophy. Fourteen years ago he first noticed delayed relaxation of his grip when he attempted to throw a hand-grenade after removing the pin, but was unable to release it. He then found difficulty in carrying weights down ladders in the fire brigade. His legs were stiff when he started to walk. Once he had to be rescued when he "froze stiff" on jumping into a swimming pool. Recently his stiffness had prevented him from working. It is well recognized that myotonia may precede dystrophic signs by several years but the interval seems too long in this case. Though there is no family history a diagnosis of myotonia

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congenita seems probable. Certainly there was no history of acute illness such as normally precedes myotonia acquisita. Patient 9, similarly, had no family history. His complaint was of delayed relaxation of hand and thigh muscles which prevented him from playing cricket (though rugby was possible as he could "work off" the stiffness in that game). However there was some loss of bulk of the right sternomastoid and the right testis, which had failed to descend in childhood, was atrophic so that a diagnosis of dystrophia myotonica seems probable. Nevertheless these two cases provided opportunities to observe the action of procaine amide on myotonic muscles which were not dystrophic.

Patient 2 was unique in that porphyria had been present for the same period as symptoms of dystrophia myotonica. Patients 3 and 6 had auricular flutter and received digitalis in full dosage while procaine amide was administered.

Methods

Procaine amide was dispensed in 0·25 gramme tablets. The initial dose in each case was two tablets four times daily (2·0 grammes/day), and this was gradually increased over a period of one week to four tablets four times daily (4·0 grammes/day). The maintenance dose was then adjusted to individual requirements (Table I).

The patients were seen daily for two weeks then at longer intervals after discharge from hospital. They were questioned about their performance of homely tasks which they had previously found difficult. The rate of relaxation of various muscle groups after strong contraction sustained for three seconds was estimated. When the hand grip was tested the wrist was fixed as described above to prevent wrist-flexion which enables myotonic patients to open their grip before the after-contraction of the finger-flexors has ceased. The electromyographic and ergographic tests used in studying the effect of intravenous procaine amide were carried out at intervals of three to four days.

Results

The effects of oral treatment of 9 patients with different types of myotonia are summarized in Table I. The decrease of myotonic symptoms and signs was of the same order as that following intravenous injection of procaine amide though, with the dosage used, control was less complete. Patient 8 was able to return to work and could swim freely in cold water. Patient 9 could play cricket, and indeed all patients noticed some or other performance in their daily life which was easier because of decreased stiffness at the onset of movement. The EMG and ergographic records con-

TABLE I.—SUMMARY OF CASES TREATED WITH PROCAINE AMIDE ORALLY.

Patient	Sex	Age Years	Duration of symptoms Years	Procaine amide Grm./day	Muscle dystrophy	Myotonic after contraction: Active	Myotonic after contraction: Active P.A.	Myotonic after contraction: Percussion	Myotonic after contraction: Percussion P.A.	E.M.G. after discharge: Active	E.M.G. after discharge: Active P.A.	E.M.G. after discharge: Percussion	E.M.G. after discharge: Percussion P.A.	E.M.G. after discharge: "Needle"	E.M.G. after discharge: "Needle" P.A.
1	M	43	11	4	++	+++	±	+	+	+++	−	+	+	+++	+
2	M	40	13	4	++	+++	±	++	++	+++	±	++	++	+++	+
3	F	44	25	4	+++	+++	+	+++	++	+++	+	++	+	+++	+
4	M	46	20	4	+++	++	+	++	++	++	±	++	++	+++	++
5	F	49	8	4	+++	+	+	±	±	++	+	+	+	++	+
6	M	54	2	2	++	+++	±	++	+	+++	+	++	+	+++	±
7	M	36	5	4	++	++	+	+++	++	++	+	+++	+	++	+
8	M	59	14	4	−	+++	±	+++	+++	+++	+	+++	++	+++	++
9	M	16	? 16	5	?+	+++	±	+++	+++	+++	+	+++	++	+++	++

+++ Severe. ++ Marked. + Just demonstrable.
± Sometimes demonstrable. − Absent.
P.A. On full dose of procaine amide.

firmed the improvement in active myotonia. A representative record before and during treatment is shown in figs. 3 and 4. As with intravenous administration there was no observable change in percussion myotonia and "needle" myotonia was still present though it was less readily induced and the repetition frequency was lower.

The effect on the myotonic phenomena was maximal one hour after each oral dose and tended to diminish in five to six hours. In all cases four tablets four times daily (4·0 grammes/day) had a significant effect. One patient with severe myotonia (Patient 6) was well controlled with two tablets four times daily (2·0 grammes/day). Another (Patient 9) required five tablets four times daily (5·0 grammes/day). There was no apparent correlation between the required dose and the severity or duration of the active myotonia or the age, sex, or weight of the patient. If the drug was withdrawn, complete relapse occurred within twenty-four hours but the same degree of improvement was regained when treatment was resumed (Patients 2, 3, and 4). Control of symptoms has been maintained for seven months.

No difficulty was experienced with digitalis therapy given concurrently to Patients 3 and 6 nor was the auricular flutter appreciably altered. Patient 2's porphyria was not adversely affected. Side-effects were noted in 5 patients but were never sufficient to contra-indicate treatment. Nausea occurred in 3 patients (Patients 1, 5, and 6), vomiting in 1 (Patient 1), and diarrhœa in 1 (Patient 4), but gastro-intestinal disturbance disappeared if the dose was temporarily decreased then slowly restored to the therapeutic level. Some patients found the slight bitter taste a little unpleasant. One patient (Patient 1) complained of feeling faint for a few minutes after each dose. There was no evidence of hypotension, even in the upright posture, and serial electrocardiograms showed no abnormality. The feeling of faintness was relieved by lying down. Treatment was not interrupted and the faintness after each dose passed off in three days. 3 patients (Patients 2, 5, and 8) noticed insomnia—either difficulty in falling asleep or a tendency to wake during the night. One patient (Patient 8) noted euphoria and occasional violent dreams, symptoms which we have noticed in other neurological patients who have had procaine amide. No skin rashes or blood dyscrasias were observed.

Discussion

A clinical trial on a small number of patients confirms that procaine amide taken by mouth is effective in controlling myotonic phenomena. It is interesting to note that percussion myotonia was only slightly diminished when active myotonia was abolished. This has also been

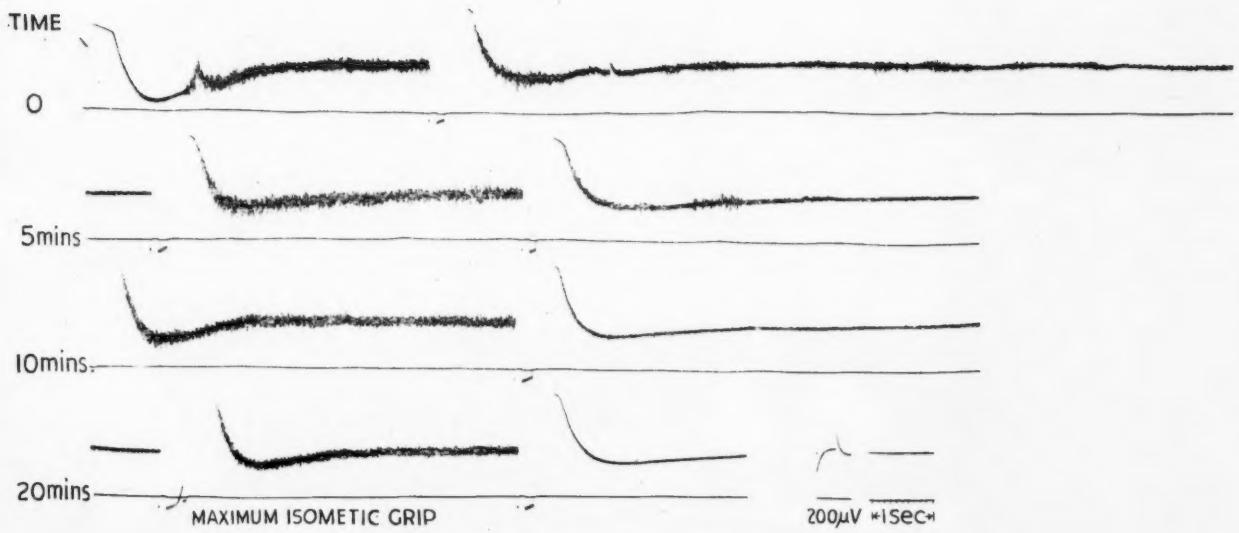

FIG. 1. (*Patient* 1).—EMG of rt. flexor digitorum sublimis. Surface electrodes. Signal artefacts at orders to "grip" and "relax." Maximum isometric grip. Records at 0, 5, 10, and 20 mins. (resting between records). Procaine amide I.V, at 100 mg. per min. started after first record.

To illustrate article by N. Geschwind and J. A. Simpson.

PLATE VII

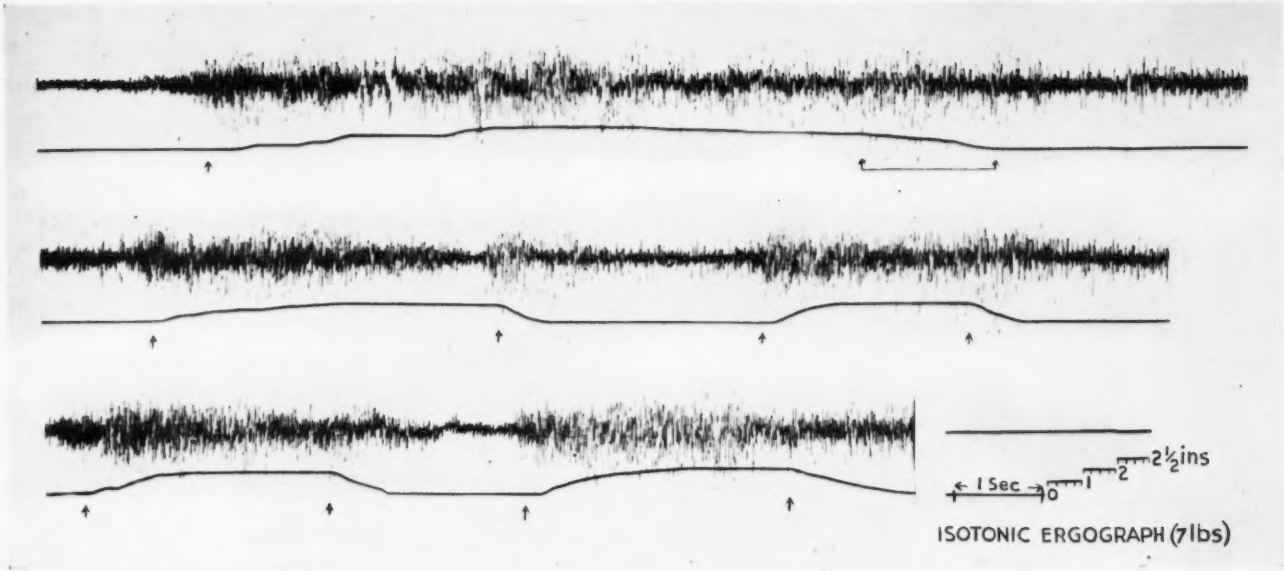

FIG. 3. (*Patient* 1).—Before treatment. Ergograph of maximum isotonic grip and EMG of rt. flex. dig. subl. Surface electrodes. Arrows at orders to "grip" and "relax."

To illustrate article by N. Geschwind and J. A. Simpson.

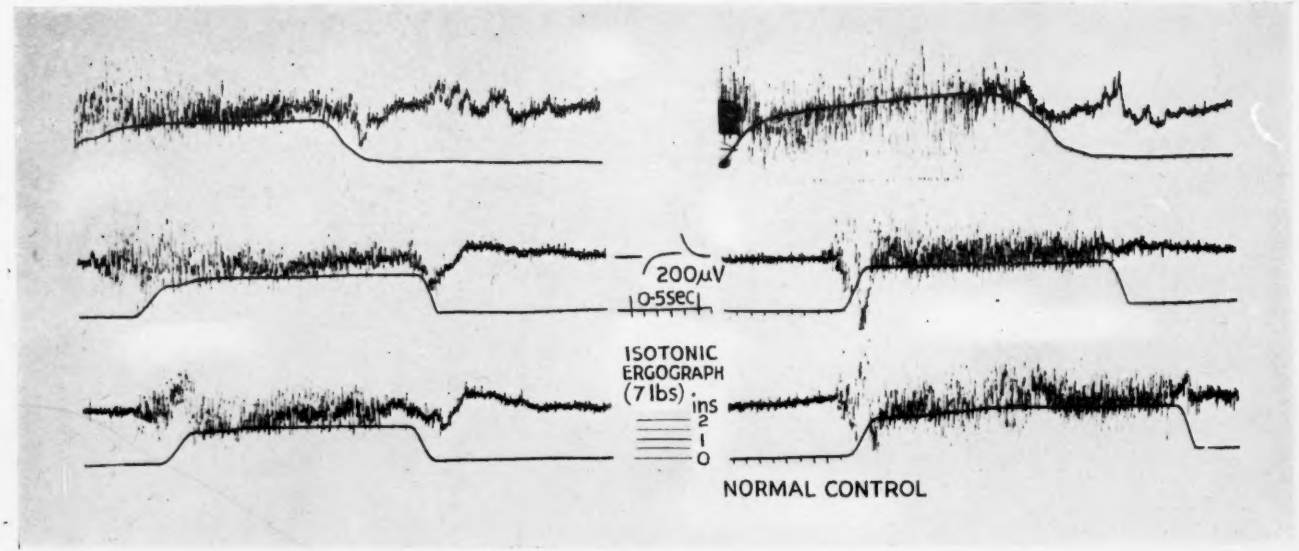

FIG. 4. (*Patient* 1).—Two hours after 1·5 grammes procaine amide by mouth. Records as in fig. 3. Three successive isotonic grips (left column) compared with a healthy control (right column).

To illustrate article by N. Geschwind and J. A. Simpson.

observed with quinine. Nevertheless our observation that "needle" myotonia was less readily induced and fired at a lower rate suggests that the threshold and accommodation of the muscle fibre are raised to direct stimulation also, though insufficient to prevent myotonic response to a gross percussion stimulus. For therapeutic purposes it is not necessary to increase dosage to the extent required to reproduce the marked anti-myotonic effect of intravenously injected procaine amide, though this may be achieved if desired. A satisfactory compromise should be reached between therapeutic efficiency and side-effects. A recommended regime of treatment is to start with one 0·25 gramme tablet of procaine amide four times daily (1·0 gramme/day). The total daily dose should then be increased by two tablets each day until the effective dose is reached. On the average this seems to be about four tablets four times daily (4·0 grammes/day) but 6·0 grammes/day may be taken with safety. The severity of the myotonia is no indication of the amount required. The first dose should be taken soon after waking as myotonia is often most severe at that time. The last dose should be taken at least one hour before retiring if insomnia occurs, or a sedative may be prescribed. It is suggested that procaine amide be given four times during waking hours as the effect is maximal in one hour and passes off in five to six hours. Further experience might show the necessity to estimate the duration of action of a single dose on individual patients and to regulate dosage accordingly. Kayden *et al.* (1951) found that a single oral dose acted for three to six hours on the heart. There has been no evidence that the drug has become less effective during the seven months of the clinical trial, but, as Schack *et al.* (1952) have noted the development of tolerance in cardiac cases, it is possible that increased dosage may become necessary.

Toxic effects have not proved troublesome. Patient 5's treatment was discontinued because of nausea at night since her myotonia was not great, her main complaint being weakness. She continued to have nausea and other symptoms without organic basis after withdrawal of all treatment. The remaining 8 patients prefer procaine amide to quinine, indeed 3 (Patients 2, 8, and 9) had been unable to tolerate quinine. Anorexia, nausea, or vomiting occurs in about 30 per cent of cases on high dosage (6–8 grammes/day) (Mark *et al.*, 1951) but can be avoided if the dose is temporarily reduced and then increased more slowly. There have been no reports of liver or kidney damage and only rare reports of agranulocytosis (Inouye *et al.*, 1951). Hypotension has not been found with oral treatment in the present series (*see also* Mark *et al.*, 1951), but we have advised a patient who complained of faintness to lie down for 10–20 minutes after taking the tablets. No significant ECG changes occur with

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the regime advised. No central stimulation has been reported hitherto with oral administration unless the drug is given in doses of 1 gramme two-hourly when hallucinations and confusion may occur (Mark *et al.*, 1951). However 3 patients in the present series developed insomnia and one noted euphoria. 2 patients had unusually vivid dreams. A patient not included in this series and not suffering from myotonia had similar euphoria, insomnia and dreams.

The side-effects described are rarely marked and sometimes only elicited by close questioning. Those patients who have experienced quinine much prefer to take procaine amide despite the slight bitter taste of the uncoated tablet. The 8 patients who continue to take it are glad to do so, being convinced that they have benefited. In some the clinical improvement has been striking (Table I). Many had not realized how stiff they were until myotonia was relieved by procaine amide. The results in a small series of cases are sufficiently promising to justify more extensive trials.

Summary

(1) Procaine amide injected intravenously in 2 patients with dystrophia myotonica abolished active myotonia, reduced "needle" myotonia, and did not appreciably alter percussion myotonia. There was no evidence of neuromuscular block.

(2) Active myotonia persisted after 80–90 per cent complete neuromuscular block with d-tubocurarine or decamethonium.

(3) It is suggested that procaine amide has a stabilizing action on the muscle membrane.

(4) A clinical trial of oral procaine amide in 9 patients with different types of myotonia confirmed its therapeutic value.

Acknowledgments

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THE SO-CALLED NUCLEUS OF CONVERGENCE

BY

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PERLIA (1889) is usually credited with the first account of a median group of nerve cells situated between the right and left oculomotor nuclei, although Bruce (1889) also independently described it in the same year. Neither attributed to this topographical feature any special function, and it is to Knies (1891) that we appear to owe the initiation of Perlia's nucleus as a mediating centre for convergent movements of the eyes. His idea was based on clinical findings in ophthalmoplegias, and it received some support on similar grounds from Stuelp (1895), Edinger (1900), Majano (1903) and other clinical observers. Perhaps, however, the concept may be said to have received its chief impetus from Brouwer (1918), whose comparative study of the oculomotor complex (compounded with examination of one pathological human mid-brain) led him to conclude that Perlia's central nucleus was characteristic only of animals capable of binocular vision. He accepted the experimental results of Bernheimer (1897) on muscle representation in the third nerve nuclei; but whereas the latter regarded Perlia's nucleus as innervating intra-ocular musculature, Brouwer associated its phylogenetic emergence with that of the Edinger-Westphal nuclei (accommodation), and hence confirmed its reputed role in convergence. Brouwer's version of Bernheimer's scheme of oculomotor organization has been figured almost exclusively in subsequent accounts, and with it the central nucleus for convergence has become widely accepted (fig. 1).

Yet criticism has not been lacking. Panegrossi (1898, 1904) found Perlia's group variable in monkeys, absent in cats, and never sharply demarcated in man. Tsuchida (1906) recorded its absence from one-fifth of the 32 human mid-brains he examined, and he considered it poorly developed in the macaque. Crosby and Woodburne (1943), in the most recent account of the primate mid-brain, had difficulty in distinguishing a central nucleus, corresponding to Perlia's, either in man or monkey. The validity of Brouwer's deductions from comparative anatomy has been

seriously weakened also by Le Gros Clark (1926), who contrasted the absence or undifferentiated nature of Perlia's nucleus in some primates, such as Tarsius and the macaque, with its exuberance in certain other mammals, like Sciurus and Tupaia, with no claim to binocular function.

Despite these damaging objections, the nucleus of convergence, as a structural and functional entity, has remained a feature of standard accounts and is propounded by many current monographs with little or no apparent misgiving (*vide*, Duke-Elder (1932), Rea (1938), Walsh (1947), Mettler (1948), Berens (1949), Wolff (1954), etc.). A few authorities, such as Adler (1953), express doubts, but the concept continues, on the whole, deeply engraven in neurological teaching. Indeed, Stutterheim (1937, 1950) had no qualms in using it as a major keystone in a new rationale of orthoptic teaching.

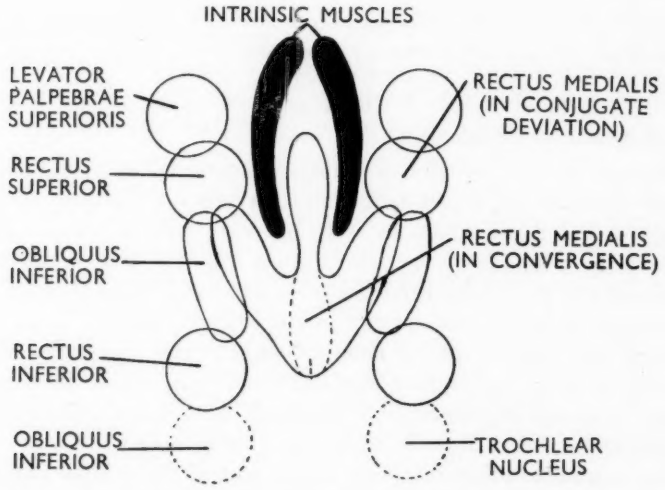

FIG. 1.—Functional organization of the oculomotor complex according to Brouwer (1918). Note proximity of motor pool of Rectus medialis to Perlia's nucleus (convergence) and radicular nature of latter.

Perusal of original contributions, with a rigorous sifting of facts from hypotheses, revealed the controversial status of this concept. In view of this, and of its neurological interest, a large series of mid-brains was examined to test its validity. The majority of these were preparations from monkeys which had been subjected to various lesions of the motor nerves of the eye and its muscles, this material thus affording experimental as well as topographical evidence.

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Material and Methods

The observations recorded below were made upon serial sections of the mid-brains of 100 monkeys (*Macaca mulatta*), two chimpanzees, and three humans. Sections of human fœtal material were also examined. All sections were cut at 10μ and were stained with cresyl fast violet, gallocyanin, silver or hæmalum and eosin. The topographical details of the median oculomotor nuclei were studied and compared in the whole of this material.

Of the monkeys 95 had been subjected to various interruptions of the oculomotor, trochlear, abducent and other orbital nerves, to elucidate the central innervation of the extrinsic and intrinsic ocular muscles (Warwick, 1950, 1953, 1954). The results of these experiments were re-examined specifically with respect to their effects upon the mid-line nerve cells of the oculomotor complex.

Each of these 105 mid-brain series consisted of several hundred sections; the material studied was therefore substantial.

Results

Topographical Observations

The right and left somatic or main oculomotor nuclei of the macaque are more compact and nearer each other than is so in the human mid-brain (cf. figs. 4 and 7, *see* Plates at end), but they are nevertheless clearly separated by a mid-line zone, the median raphe. This is a complex arrangement of axons, dendrites, and neuroglia, which also contains nerve cells, mostly multipolar and variable in size and in number.

At caudal levels of the oculomotor complex this intermediate zone is wide dorsally in the macaque, chimpanzee and man. Hence, in transverse sections, it has the appearance of a cuneiform mass, as if driven in between the oculomotor nuclei from the direction of the aqueduct (Plate IX, fig. 2). Situated centrally within this wide caudal part of the median raphe is a dorsal unpaired group, the caudal central nucleus. This consists of multipolar neurones smaller than those of the chief oculomotor mass (cf. figs. 8 and 9), the cells being less compactly arranged in the chimpanzee and man than in the monkey, where they form a highly distinctive feature (fig. 2). This nucleus is usually accepted as Perlia's "diffuse nucleus of the mid-line" (his original description referred to man). In its dorsal and caudal position it certainly does not correspond with his better known central nucleus (of convergence). In addition, it has been shown that the caudal central nucleus innervates the Levatores in monkeys (Warwick, 1953*a*). The same nucleus appears to be identical with the posterior dorsocentral nucleus of Panegrossi (Warwick, 1953*b*).

In addition to this caudally situated median nucleus all the material examined also showed a clearly differentiated median nucleus at a level immediately above, or cranial to, the main oculomotor nucleus (fig. 3). This, the group which Perlia (1889) called *nucleus medianus anterior,* was composed of small multipolar cells like those of the Edinger-Westphal nuclei (fig. 10). The latter bilateral columns were seen to fuse cranially to become continuous with the anteromedian nucleus. This topographical continuity has been noted by others, and experimental evidence to show that the anteromedian nucleus is also, like the Edinger-Westphal groups, a parasympathetic component of the oculomotor complex, has been reported elsewhere (Warwick, 1954).

These two median nuclei, at the caudal and cranial extremities of the third nerve complex, were constantly and easily identified in all series inspected. They have been described at some length because they may be confused with the central nucleus with which Perlia's name has been usually associated. This, by its supposed significance in convergence, has become more familiar than its caudal and cranial fellows. All three were described by Perlia (1889), and it is plain from his account and diagram (fig. 15) that the central nucleus was to be found at intermediate oculomotor levels and situated ventrally in the median raphe. He likened its cells to those in the main oculomotor nuclei. These points require emphasis, because in some topographical accounts descriptions of Perlia's nucleus have diverged considerably from his original account both as regards situation and cytological details.

It will be evident from the preceding descriptions of the caudal central and anteromedian nuclei that these, in fact, do not correspond either in site or cell type with Perlia's nucleus, which was obviously to be sought at some intermediate level between them. Attention was therefore next directed to this region.

Examination of the median raphe in 100 macaque mid-brains showed variable conditions. It may be stated at once that cranial to the caudal central nucleus no discrete median mass, of any kind of nerve cell, was ordinarily seen between the main third nerve nuclei, although, as will become apparent, such a feature was observed in a small minority (cf. figs. 4 and 5). At all such levels the zone between the main oculomotor nuclei contains somatic motor neurones, indistinguishable from those in these nuclei, except where these masses are closely approximated at their cranial ends. Smaller cells of two types, were also found in the raphe. A multipolar neurone, of intermediate size and identical with the cells of the caudal central nucleus, was often seen in small numbers in the mid-line at levels cranial to this group, of which they were evidently detached

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members. Such a cranial extension of the caudal central nucleus is more marked in human and chimpanzee mid-brains, and despite its dorsal position in the raphe, it has been confused with Perlia's central nucleus (fig. 6). Cells of this type were rarely found in the ventral region of the median raphe. A smaller cell, described as ganglionic by some authorities, was also seen in considerable numbers in the raphe in its caudal two-thirds. Though usually scattered, they were occasionally aggregated in small median groups; but serial sections demonstrated the trivial dimensions and inconstancy of such arrangements.

Neither of these small nerve cell types could be regarded as representatives of the classical Perlia's nucleus, either in topographical distribution or, as will be seen, in their functional significance. Attention was therefore concentrated upon the large, somatic motor nerve cells of the median raphe.

At high cranial levels few somatic motor neurones were found in the mid-line, nor were they ever numerous in the ventral part of the raphe at caudal levels in the oculomotor complex. Between these extremes, however, where the right and left third nerve nuclei are relatively close, this kind of nerve cell was always to be detected in considerable numbers in the median raphe (fig. 4). The arrangement of these motor cells was somewhat variable, but a prolonged study and comparison of the large amount of material at hand permitted some degree of uniformity in the pattern of their grouping to be observed.

The commonest disposition of these somatic motor cells, which were frequently aggregated in small groups, was not strictly in the mid-line, but in a paramedian position, as if a few of the most medial cells of the third nerve nucleus were separated from their fellows and pushed into the median raphe (fig. 4). Such groups did not usually cross the median plane; they were sometimes bilaterally symmetrical, but not usually so. Paramedian groups of this kind, variable in size and definition, were observed in all the macaque mid-brains examined. Frequently a substantial part of the ventral column of the oculomotor nucleus, adjacent to the raphe, was clearly distinguishable as a paramedian group, as if cleft from the dorso-medial aspect of this column. Less often, in the caudal third of the dorsal oculomotor column, where it lies antero-lateral to the caudal central nucleus, a dorso-medial moiety of the mass was distinguishable as a separate topographical entity.

It is important to emphasize hat these paramedian subdivisions of the oculomotor nuclei evinced, when followed through serial sections, a marked lability, separating from and rejoining adjacent cell masses at successive levels in an irregular manner. This perhaps explains the finding

that a paramedian group was not usually matched by a contralateral fellow, and also accounts for the fact that a cursory examination of a few specimen sections from a mid-brain series may fail to demonstrate the uniform occurrence of this sort of subdivision in the macaque.

In a minority only of the monkey mid-brains was it possible to make out a substantial unpaired mid-line nucleus corresponding to Perlia's (fig. 5). The criteria employed were that it must be a discrete median group, showing topographical constancy through many succeeding sections. In 9 of the 100 series studied these criteria were fulfilled. The central nucleus observed was always situated ventrally in the raphe in about the intermediate third or so of the cranio-caudal extent of the oculomotor columns. In a further 14 series a median group was visible in some sections only, forming and disappearing in a protean manner when traced through adjacent serial sections.

A critical survey of the material available thus demonstrated that the oculomotor centres examined with respect to the incidence of a nucleus of Perlia could be roughly classified as follows:

(*a*) Those showing paramedian groups only: 77 (77 per cent).

(*b*) Those with, in addition, a transitory median nucleus: 14 (14 per cent).

(*c*) Those showing a well-developed median nucleus: 9 (9 per cent).

Obviously such a classification can only be approximate, and is chiefly of value in indicating that a median nucleus answering to Perlia's description is not more than an occasional anatomical feature of the macaque's mid-brain. In fact, comparison of different series demonstrated a continuous gradation from those with purely paramedian groupings to a small fraction showing a true central nucleus. All degrees of intermediate differentiation were found, and it was possible in some instances to trace the formation of transitory median nuclei by fusion of bilateral paramedian groups. Moreover, where a well-defined median mass was found, paramedian groups were lacking. Both appeared to be different grades of the same fundamental pattern of arrangement. For these reasons it seemed possible to presume that the same factors which cause detachment of paramedian groups of cells from the median aspect of the main oculomotor nuclei might also be responsible for the formation of a median nucleus, when present.

Attempts were therefore made to discover any structural details of the oculomotor region which might indicate such factors. For example, some of the vessels supplying it were seen to travel considerable distances in a dorso-ventral direction in the raphe (figs. 2 and 5), but only occasionally were these so distributed that they could be considered the cause of

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separation of paramedian groups. No instance of a true median nucleus demarcated from adjacent cell masses by vascular arrangements was encountered.

It might be supposed more probable that, as in other parts of the central nervous system, the disposition of nerve fibres, particularly between the oculomotor nuclei in this instance, would prove to be the major influence in creating minor subdivisions. Even in Nissl-stained material it was evident that large numbers of nerve fibres traverse the median raphe in a dorso-ventral direction (fig. 7). In sections stained specifically for fibres it was clear that bundles of fibres occupied the intervals between paramedian or median sub-groups and the main oculomotor nuclei (fig. 17). Many of these axons appeared to be derived from the Edinger-Westphal nuclei, and to constitute what Bernheimer (1894) called *fibræ rectæ*. The amount of suitably stained material available in this research was not, however, considered adequate to decide this point, which will receive attention in a later report.

In the human and chimpanzee series scrutinized the oculomotor complex was found to be broadly similar to conditions in the macaque, but some topographical differences were noted. In both the former species the whole complex, like the mid-brain itself, was observed to be relatively broader, the median raphe being wider, especially at caudal levels. Perhaps the less compact nature of the caudal central nucleus in these forms, in which it is also situated further ventrally than in the monkey is associated with this spaciousness. Paramedian groups were not so regularly observed in human or chimpanzee series, a finding perhaps related to the commoner occurrence of a representative of Perlia's nucleus in such material. In the admittedly limited number of series examined, however, though large motor cells were always present in the median raphe at intermediate oculomotor levels, they were never numerous and not always compactly aggregated (figs. 6, 7 and 11). They were often irregularly scattered, but were the only elements observed which could be construed as representing Perlia's central nucleus.

To summarize, topographical study showed that a median nucleus (of Peria) is usually absent in the monkey, though discernible in a minority of mid-brains. When it occurs, however, it is more compact and discrete, in the experience of this report, than the poorly defined mid-line group which can usually be traced in human and chimpanzee material.

Experimental Observations

The findings detailed below were derived from study of mid-brains of 95 monkeys submitted to various orbital and intracranial interruptions of

the oculomotor nerve and its branches. These were examined in serial preparations with special reference to the following questions:

(1) Are the nerve cells of a central nucleus of Perlia, where this exists in the monkey, a radicular source of oculomotor fibres or not?

(2) Do the neurones of such a nucleus show retrograde degeneration following denervation of the Rectus medialis?

(3) If not situated in Perlia's nucleus, in part or whole, what is the locus of the motor pool of the Rectus medialis?

(4) Does interference with the nerve supply of any other extra-ocular muscle produce observable changes in the central nucleus?

(5) Does peripheral interruption of the reputed ocular parasympathetic pathway cause changes in the nucleus of Perlia?

These several questions will be answered *seriatim*, but attention must first be drawn to one difficulty: since only a minority of the mid-brain series examined contained a distinguishable central nucleus of Perlia, it could not be ensured in advance that the most significant experiments were carried out on the minority of animals possessing this feature. It was fortunate that such a nucleus proved to be present in several monkeys which had been subjected to particularly suitable injuries, such as denervation of the Rectus medialis. However, other experiments, at first sight less directly critical, also contributed significant facts.

(1) Of seven monkeys submitted to unilateral oculomotor nerve division within the cranium, only one possessed a distinct nucleus of Perlia. Many of the motor nerve cells of this median group showed retrograde changes. In all seven series paramedian groups of cells, contralateral with respect to the side of division, displayed similar changes, which have been detailed previously (Warwick, 1953*a*).

Counts of the extent of chromatolysis in this material showed that 42 per cent of the total population of the somatic oculomotor nuclei (i.e. excluding the Edinger-Westphal and anteromedian nuclei) reacted to unilateral divisions. These would be expected to involve not more than 50 per cent of the cells in the bilateral oculomotor mass. The criteria of retrograde degeneration used in this study were stringent (Warwick, 1950), and hence is was judged improbable that many of the oculomotor nerve cells were other than radicular components of the third nerve.

(2) Four monkeys subjected to extirpation of the Rectus medialis exhibited in sections some sort of central nucleus, and in two of these animals this was sufficiently well-developed to be regarded as a nucleus of Perlia. In none were cells of the central nucleus, or of paramedian groups,

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involved in the retrograde changes. In one of this series the central nucleus was striking in size and definition, and the contrast here, between normal cells in it and chromatolytic cells in the adjoining main oculomotor nucleus, was particularly clear (fig. 13).

(3) As previously reported (Warwick, 1953*a*), extirpation of the Rectus medialis regularly produces a retrograde response in the ipsilateral oculomotor nucleus. These changes were confined to nerve cells in the ventral subdivision, and in no case were they observed in paramedian groups, or any other part of the oculomotor complex (fig. 13).

(4) These negative findings, concerning innervation of the Rectus medialis from Perlia's nucleus, naturally provoked an enquiry into the destination of the axons of this group. Over 50 series in which the other four extra-ocular muscles supplied by the third nerve had been excised were available for observation.

Experiments upon the Rectus inferior and Levator never caused retrograde changes in a median nucleus, when present, or in paramedian groups. On the other hand, as noted elsewhere (Warwick, 1953*a*), the nerve cells innervating the Rectus superior were regularly observed to lie in the paramedian zone of the contralateral oculomotor nucleus. At caudal levels the paramedian part of the dorsal oculomotor nucleus, which has been described already as sometimes forming a topographical entity, appeared to consist almost exclusively of neurones supplying this muscle. At intermediate levels chromatolytic cells were scattered in the smaller paramedian groups referred to above. In two series a central nucleus was present, and in both considerable numbers of its cells were also affected (figs. 12 and 14).

Regarding the remaining muscle, the Obliquus inferior, it was observed that, whereas its main motor pool lies in the lateral oculomotor mass, as detailed previously (Warwick, 1953*a*), some of its radicular nerve cells mingle with those of the Rectus superior, in paramedian groups and the central nucleus, when it occurs. These degenerating cells were, however, ipsilateral, and were never as numerous as those affected by denervation of the Rectus superior.

(5) In view of observations recorded by certain workers, the effects of lesions of the ocular parasympathetic pathway upon cells in the median raphe was checked. Of five animals subjected to ciliary ganglionectomy one only showed a distinct central nucleus, and no changes were evident in this, nor were they seen in paramedian groups in the other series. As has already been reported (Warwick, 1954), experimental lesions of the ocular pre-ganglionic parasympathetic axons produce changes only in the

Edinger-Westphal and anteromedian nuclei, which are composed of nerve cells distinct in type from those which form Perlia's nucleus.

Discussion

Binocular movements may be categorized for convenience as conjugate deviation, convergence, and divergence, according to whether the visual axes are moved in parallel, made to approach each other to intersect at a near object, or moved apart again for more distant fixation. Confusion sometimes arises, however, over the term divergence, which is sometimes called "negative convergence." This usage seems misleading, for convergence and divergence are evidently the same process in opposite phases, both being equally exact and active in performance. Divergence is also sometimes applied to divarication of the visual axes beyond parallelism, an abnormal relationship incompatible with binocular vision. We are concerned here, however, with normal function, and divergence will invariably signify separation of the visual axes towards parallelism in this discussion.

All binocular movements must be harmonized with extreme nicety, since even a small lapse from the concerted action of the extra-ocular muscles at once produces diplopia. Yet we have little direct information upon the activities of the peripheral neuromuscular structures involved, except for certain experiments by Sherrington (1905) and Szentágothai (1950). Most investigators, like clinical observers, have been concerned with ocular movements, rather than muscles, and their conclusions therefore throw no direct light upon what actually occurs in peripheral neuromuscular structures. Regarding the central nervous apparatus concerned a wealth of hypothetical deduction from clinical manifestations exists in the literature, but satisfactory factual information is scanty, considering the weight of supposition it has been made to bear.

Despite the lack of established data it is inevitable to postulate neuronal dispositions to make possible the integration of concerted ocular movements, but this scarcely justifies the elaborate array of "centres" which have been invented to explain certain abnormalities of ocular motor function. The pathological evidence for these centres has never been convincing, as Riley (1930) pointed out, and they remain largely unsupported clinical conceptions. Perhaps they have their roots also in artificial and over-simplified views of ocular movements, in the analysis of which it is customary to think primarily of motions in certain geometrically simple directions. This has led to "yoking" of pairs or other limited groups of muscles either in synergy or antagonism. Although the involvement of other ocular muscles less prominently in the same move-

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ment is sometimes implied, it is less often overtly stated. Yet it is a logical consequence of the anatomical attachments of the ocular muscles, and of orthodox muscle physiology, that all the extra-ocular muscles take part in any binocular movement. Readjustment in the tensions of all twelve muscles must be so precisely integrated that single vision is maintained, whatever the direction of gaze. Transference of gaze entails not merely re-direction of the visual axes but also, quite commonly, a change in their inclination to each other. It is evident, therefore, that the degree of activity in any one muscle cannot bear a constant ratio to the amount of contraction or relaxation in others, as might conceivably hold if all eye movements were deviations of constantly parallel visual axes. Such unvarying interaction would not permit the alternate convergence and divergence inseparable from fixation upon successive objects at different ranges, and it is obvious that the distribution of tensions in the ocular muscles must be ordered by mechanisms of plasticity as well as precision. Whatever their nature they must be sufficiently labile to ensure the maintenance of corresponding points on both retinæ in any position of the eyes.

Convergence and divergence can be separated only in artificial analysis from the constant background of conjugate deviations, upon which they are, as it were, superimposed. Common observation shows that vergence movements are rarely pure, being at most times compounded with some degree of elevation, depression or deviation of the visual axes. Slight torsional effects of most of the ocular muscles must also be taken into account, for these must be so controlled that the constant inter-retinal relationship required for binocular vision is sustained. Even if we omit head and neck movements, which might be said to provide a sort of "coarse adjustment" in shifting the direction of regard, it becomes evident that an intricate and widespread central integration must exist. Clearly this apparatus develops its full delicacy of action only in conjunction with use and experience, for the neuromuscular skill required for binocular movement is learnt after birth and is perfected in an inseparable partnership with the sensations of vision. It would be surprising, therefore, if ocular mobility were not organized in part at least from cerebral levels.

In view of these considerations it is perhaps curious that convergence should have been singled out from the rest of binocular activity, and assigned, moreover, a mid-brain centre. If only to provide a means for voluntary initiation of eye movements it is inevitable that mesencephalic centres, whatever their nature, must be subservient to cerebral influences; and if, as seems probable, the adroit refinement of these movements is dependent upon cerebral patterns of integration, the supposed mid-brain

centre for convergence assumes a lesser role than its description suggests. Precisely what those who have favoured this concept had in mind concerning its functions must therefore be asked. The majority of recent writers are vague upon this point, and the expression "nucleus for convergence" appears to have been copied from text to text over many years with little critical enquiry into its sources.

To postulate some sort of unpaired or median control of bilateral structures in intimate association seems at first sight plausible, but it is difficult to follow why this should be required for convergence and yet not for other binocular co-ordination, though it is true that a centre for divergence has been suggested (Holmes, 1921). A median brain-stem centre has not been regarded as necessary in connexion with other motor nuclei concerned in bilaterally organized movements, such as those of speech, mastication, and the like, nor have specific median nuclei for their integration been described. The only unpaired localized arrangement which might be thought an example is Broca's area, and this, be it noted, at a cortical level. These theoretical objections are the more pertinent because the original protagonists of the nucleus of convergence themselves relied so extensively on hypothesis. Apart from a slender substance of fact, the endowment of Perlia's nucleus with this property was founded on nebulous premises.

A few earlier authors have been more exact in their ideas of the precise action of the cells forming Perlia's nucleus. In Bernheimer's schema of muscle representation (1897), the motor pool of the Rectus medialis was placed just lateral to the central nucleus. This proximity may have influenced Brouwer (1918), whose slightly modified version of the same schema is better known, though his main argument rested on comparative data. He differed from Bernheimer's view of the central nucleus as a source of ocular parasympathetic supply, picturing it as a second and conjoint motor pool for the Recti mediales when acting together in convergence, as had Edinger (1900), Majano (1903), and von Monakow (1905) before him. It was apparently the belief of these authorities (except Bernheimer) that during conjugate movements the contracting Rectus medialis was innervated from its own separate lateral motor pool, and not from the convergence centre, despite the fact that the visual axes must be as accurately converged in conjugate deviation as at other times. Their diagrams, like Perlia's (1889), which itself was strictly topographical (fig. 15), showed axons from the central nucleus entering the third nerve; but they went further in consigning these fibres to the Recti mediales, which were depicted as receiving fibres also from the main oculomotor mass. Such a duality of lower motor neurone supply, if true, would be unusual and

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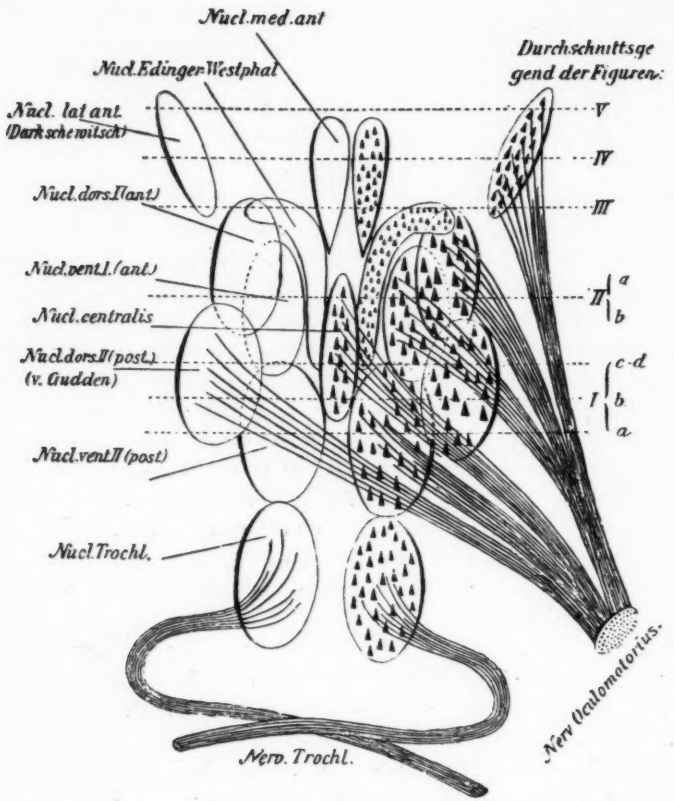

FIG. 15.—Perlia's diagram (1889) of the topographical subdivisions of the oculomotor nuclei (as seen from in front, i.e., ventral aspect). Note that the nucleus centralis (="nucleus of convergence") is shown at an intermediate level and as contributing axons to the third nerve. The antero-median nucleus (nucl. med. ant.) is depicted as bilateral, unlike subsequent descriptions.

perhaps unique. The conception certainly seems unnecessarily complicated and difficult to parallel elsewhere in the central nervous system.

Thus it transpires that the protagonists of the so-called centre for convergence were in reality concerned with a mid-line nucleus described as the joint motor pool of the Recti mediales. It would be quibbling to object to the labelling of such a group as a "centre," for this term has in its wide application acquired an elasticity which robs it of much meaning. But in this instance something more than a common central origin of the efferent paths to two muscles was obviously intended, and the description

"nucleus of convergence" has come to signify a degree of mutual control or integration which would not be expected in a pure group of lower motor neurones. The term "control" has also, of course, been loosely applied to the influence of motor neurones upon their muscles, a usage conductive to fallacious thinking, for both anatomically and physiologically these cells are merely vehicles of communication, by which other elements in the nervous system project their patterns upon the musculature. That lower motor neurones could in themselves organize the fine synergy exhibited by the Recti mediales, or amongst any ocular muscles for that matter, is contrary to neurological precept. Nevertheless, scrutiny of the main sources of the still current belief in a centre for convergence in Perlia's nucleus reveals this very concept.

The central nucleus might have been accounted more reasonably as consisting in part at least of internuncial neurones, subserving reciprocal innervation and perhaps more plastic connexions between the efferents of the Recti mediales. This possibility has received little attention, and it must be admitted that Perlia's nucleus, when present, seems in man, ape and monkey scarcely adequate for a finely graded integration between even the Recti mediales. Since other muscles are also involved in convergence, it becomes still more difficult to believe that such a comparatively small number of cells could mediate their interactions.

The foregoing considerations indicate that the concept of a convergence centre in Perlia's nucleus was subject *ab initio* to radical objections, but these have been largely overlooked and the measure of acceptance accorded the idea has obscured the dubious nature of its origin. Setting aside, however, theoretical criticisms, the validity of this concept may be examined from two complementary standpoints: (i) topographical, and (ii) functional. Unless the evidence on both counts proves adequate and uncontradictory in animals possessing the faculty of convergence, the belief that Perlia's central nucleus is a centre for this must be declared erroneous.

The topographical observations of this study were in general agreement with the reports of Tsuchida (1906), Le Gros Clark (1926), and Crosby and Woodburne (1943) in the finding that Perlia's nucleus is by no means a constant or impressive feature of the oculomotor complex in primates, including man. Few would venture to deny the monkey a high measure of accurate binocular vision; yet in this animal a recognizable central nucleus of Perlia was found to be unusual in this study, nor was the group impressive in differentiation or size in the chimpanzee and human material examined. An assertion that one fifth of mankind lacks the power of convergence would be justly rejected, and yet Tsuchida (1906)

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found Perlia's nucleus absent from just this fraction of the human midbrains examined by him.

Evidently in anthropoids the parallel between the development of Perlia's nucleus and the evolution of convergence urged by Brouwer (1918) is untenable, and Le Gros Clark (1926), in a broader comparative series, found other anomalies which cast grave doubts upon Brouwer's phylogenetic arguments. Indeed, one would have expected that his observations would in themselves have proved sufficient to dismiss Perlia's nucleus as a centre for convergence. This concept was, however, already so far accepted that neither then nor since has any progress been made by the facts of comparative and topographical study, although they have now accumulated for half a century in contradiction.

It might be expected that some enlightenment might be shed into these phylogenetic difficulties by an appeal to the ontogeny of the oculomotor group, but a careful comparison of the main embryological studies, by Tsuchida (1906), Paton and Mann (1925), Mann (1927), Pearson (1944), and Cooper (1946), produces no consistent picture of the origin and development of the nucleus of Perlia. Tsuchida (1906) and Pearson (1944) found it variably differentiated and sometimes unidentifiable in human fœtal material; the latter, like Le Gros Clark (1926), considered the nucleus a detached paramedian part of the main oculomotor mass. Mann (1927) and Cooper (1946), despite different views of its precise derivation, figured it in embryos (at 35 mm. and 19 mm. respectively) as a median mass at one stage joining together the third nerve nuclei. Since neither of these observers mentions the caudal central nucleus, which Pearson (1944) described as a more prominent feature in the human fœtus, it is not always certain that their median groups were in fact Perlia's nucleus. It is interesting that both detected a median nucleus well before subdivision of the main oculomotor nucleus into its dorsal and ventral parts (at 48 mm. and 35 mm. respectively), for if this ontogenetic sequence of events were phylogenetically significant, we should be confronted with the enigma of a central nucleus, reputedly for convergence, in vertebrates prior to Ganoids and Teleosteans, for in these forms the oculomotor nucleus already presents dorso-ventral subdivision. Mann (1927) apparently overlooked this fundamental contradiction, but was particularly concerned to explain why the median nucleus, for convergence, should precede in ontogeny the Edinger-Westphal nucleus, for accommodation. These discrepancies depend, of course upon the validity of the recapitulation theory in this special instance; but meanwhile the evidence here remains adverse concerning the central nucleus for convergence. Embryological details of this nucleus in vertebrates other than man, which

might help to clarify these obscurities, are not available. It would, for example, be of interest to know whether a median oculomotor nucleus is a common feature and whether it appears in the embryos of species which do not display it after birth.

It is evident that the embryological data so far recorded, though admittedly inadequate, lend no support to the concept under discussion, tending rather to add to the gravamen of the anatomical denial.

Since the belief in Perlia's nucleus as a mediator of convergence fails to carry conviction on purely anatomical grounds, the second criterion of its validity—the function of its constituent nerve cells—must next be considered.

In previous papers (Warwick, 1950, 1953*a*) it was demonstrated, in macaques, that the axons of nerve cells in the median raphe do enter the third nerve. Re-examination of this material has confirmed that the fibres of nerve cells forming a nucleus of Perlia do indeed leave the midbrain in the oculomotor trunk, as has been widely accepted in the past. Perlia's nucleus, therefore, when it exists in the monkey, is not a collection of connector neurones. Its cells, on the contrary, were observed to be radicular, innervating the Rectus superior and, to a lesser degree, the Obliquus inferior. Both are said to be able to adduct the eyeball, but it was the clear and constant finding of this research that Perlia's nucleus does not innervate the Recti mediales, whose separate motor pools have been shown to lie ventrally in the main oculomotor nuclei (Warwick, 1953*a*). It must therefore be concluded that experimental results also contradict the notion that Perlia's nucleus has any particular significance in convergence. Certainly it does not provide a second and conjoined motor pool for the Recti mediales.

Bernheimer (1897) and more recently Foerster, Gagel and Mahoney (1936) have claimed that Perlia's nucleus supplied intrinsic ocular musculature, especially the Ciliaris oculi. In view of the accommodative activity of this muscle some writers have seen in this further testimony to the association of the nucleus with convergence. In this connexion it is to be noted that Mann (1927) considered that the Edinger-Westphal columns were derived from the same embryonic median mass as Perlia's nucleus. The usual view, however, is that the ocular parasympathetic supply has its source in the Edinger-Westphal nuclei, and extensive evidence has been presented elsewhere (Warwick, 1954) in corroboration of this.

To summarize, theoretical considerations and the observations of comparative, topographical, and experimental anatomy combine to reject the description of Perlia's nucleus as a centre for convergence.

From this conclusion two questions naturally arise: firstly, if not con-

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cerned with convergence, what is the significance of Perlia's nucleus; and secondly, is the concept of a "centre for convergence," in the customary connotation of such terms, a sound hypothesis?

The basis of fact presented here provides no final answer to either question, but certain probabilities do emerge from the foregoing discussion. Regarding the former question, it is suggested that the comparative and developmental details available point to the central oculomotor nucleus as a product of mid-brain growth mechanisms. When the oculomotor groups develop from the basal laminæ of the mid-brain they are at first well separated, but as these two cell masses proliferate they bulge dorsally into the cavity which will become the aqueduct. As a result of this bilateral bulging the laminæ become sharply angled at their median junction, and as their aqueductal surfaces approach each other, a deep median cleft develops between them. This is ultimately obliterated by fusion, the zone between the two much more closely approximated oculomotor nuclei marking the former position of the cleft (fig. 16). The same

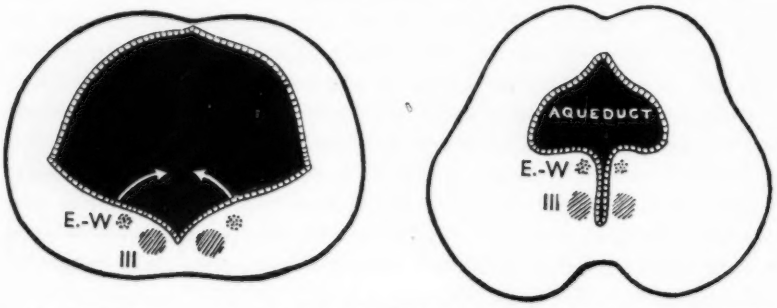

FIG. 16.—Diagrams showing how the folding of the basal laminæ of the human embryonic mid-brain may produce an approximation of the somatic oculomotor masses and a change in the position of the visceral, Edinger-Westphal columns (E.-W.), from a lateral to dorsal position.

growth processes would account for the final position of the developing Edinger-Westphal nuclei dorsal, or even dorso-medial, to the somatic oculomotor masses if, as is usually stated, these visceral groups arise further laterally in the basal laminæ. Fusion of the oculomotor nuclei across the mid-line may be in part a consequence of their approximation and also of proliferation of their cells. Le Gros Clark (1926) has noted a phylogenetic tendency to an increase in the number of oculomotor neurones in higher forms. The growing axons of the Edinger-Westphal nuclei have to pass ventrally to enter the third nerve, and in adult primate material it can be seen that many do so by traversing the median raphe,

FIG. 17.—Transverse section of adult human oculomotor complex, showing the dorso-ventral direction of nerve fibres in the median raphe which separate Perlia's nucleus (P.) from the main third nerve nuclei (III). The section is stained by the Weigert-Pal technique, and hence fibres appear black and groups of nerve cells show as pale areas. The Edinger-Westphal columns (E.-W.) are prominent. × 15.

forming the *fibræ rectæ* of Bernheimer (1894) (fig. 17). If these axons do not decussate, and evidence of this has already been recorded (Warwick, 1954), it is not difficult to visualize the two groups of fibres cleaving a median nucleus from a junctional mass of nerve cells between the third nerve nuclei. Moreover, in species whose right and left nuclei are more closely juxtaposed, like the macaque, bands of ventrally running fibres might equally well separate off the paramedian groups so characteristic of this animal. It is also possible to explain in this manner, the inconstant occurrence and loose arrangement of the paramedian groups noticed in the human and chimpanzee series of this research, for in both forms the median raphe is more spacious than in the macaque. These views are, however, merely suggestions, and further embryological observation is required to elucidate such points.

Finally one may enquire whether some other centre exists, in the midbrain or elsewhere, for the integration of convergence. Although this study affords no positive evidence concerning this, it is not out of place to raise certain issues, for these have a direct bearing upon the concept under

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discussion. If in fact there is some mode of control of the Recti mediales peculiar to their integration in convergence, as distinct from other mechanisms concerned with these muscles in movements of conjugate deviation combined with convergence, it is unavoidable to postulate a "higher" apparatus capable of a unified organization of both systems of control. For it is common experience that binocular fixation upon an object can be maintained without trace of diplopia during movements of the head from side to side, or indeed in any direction, even though exaggerated beyond normal habit. The transition between both systems of control, if they can normally be regarded as separable, is obviously imperceptible. It is true, of course, that certain clinical manifestations have been recorded which are characterized by apparent dissociation of convergence from other ocular movements; but these are obscure and pathological states, and it is highly dubious whether such rare peculiarities should be advanced in evidence of a specific centre for convergence in the normal. Even if there is some particular means of controlling convergence, its nature remains uncertain. Regarding this, and also the larger issue of the total integration of the ocular muscles, it is perhaps fallacious to seek the rather localized arrangement implied by the word "centre"; for this term, as customarily used, appears to set undue emphasis upon the cell bodies of neurones, compared with their processes. It is scarcely necessary to point out that any pattern of integration conducted by groups of nerve cells must depend not merely upon the distribution of their cytons but perhaps even more upon their connexions. These commonly take the form of tracts of varying lengths connecting concentrations of nerve cells jointly involved in some form of mediation between the afferent and efferent conductors. It is obvious that very localized damage may, by interruption of some part of this organization, produce characteristic effects, often of signal value in the diagnosis of disease. But it is surely misleading to confuse a restricted site of destruction with a widely extended system of neuronal control, thus compressing the functions of the whole into its damaged part. For such reasons, which form a cardinal objection to the supposed functions of Perlia's nucleus, it is perhaps equally vain to search for a substitute in any other group of nerve cells. Such mid-brain concentrations as the interstitial nucleus, the nucleus of Darkschewitsch, and others in the vicinity of the oculomotor complex have been from time to time associated with ocular motility. Perhaps it would be cynical to point out that these are bilateral groups and thus unattractive to those in quest of a centre for convergence. It is certain that none of these nuclei contribute fibres to the third nerve (v. Warwick, 1953*c*), so that they might be internuncial elements in neuronal

networks serving integrations of ocular movements; but the evidence concerning all of them is unsatisfactory and controversial.

The occurrence of internuncial neurones in the oculomotor nucleus itself has been occasionally suggested, and Lorente de Nó (1947) has described such cells in rabbits with some detail. They cannot be numerous in the monkey, for at least 84 per cent of its oculomotor nerve cells are radicular, and even if the remaining fifth were internuncial it is improbable that so small a fraction could mediate the fine degree of integration characteristic of the ocular muscles.

The rapid and labile response of the visual apparatus to the endlessly varying demands made upon it suggests an extremely intimate and inextricable relation between the visual content of consciousness and the motor functions of the eyes. To look therefore at mesencephalic levels alone for a supposedly autonomous centre controlling convergence, which may justly be regarded as the ultimate perfection of binocular movement, is basically unphysiological. It seems that we have in the convergence centre a notion originally conceived on meagre grounds and perpetuated with little critical evaluation of its implications. By its superficial attractiveness and the nebulous terms in which it is usually framed, this hypothesis has evaded the onslaught of much adverse criticism, to survive as an interesting example of neurological mythology.

Whether a controlling mechanism for convergence is to be found at brain-stem or cortical levels, localized in some sort of "centre" or disseminated in a complex integration of both, it is claimed here that the evidence presented has proved that the nucleus of Perlia exercises no such function in the monkey. In view of the close similarity of the visual apparatus in higher primates, it seems improbable that it would do so in man.

Summary

The concept of a median centre for convergence in Perlia's central nucleus has received wide acceptance in neurological and ophthalmological literature; but when original papers are examined the foundations of this concept prove markedly insecure.

Theoretically the idea of such a centre can be shown to be radically unsound. Its conception and uncritical propagation from text to text have been due in part to misconceptions and imprecisions regarding such terms as "centre" and "control," and in narrow views of the co-ordination of the ocular muscles.

The chief factual basis for the concept has resided in a supposedly close parallel between the development of the nucleus of Perlia and the emergence of binocular vision. For more than half a century topographical

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and comparative studies of the oculomotor nuclei have provided many contradictions to this.

The topographical observations of this research have shown that Perlia's nucleus is not usually found in the monkey's mid-brain, and have also confirmed the poor development of this feature in the chimpanzee and man, despite the possession of binocular function in all three forms.

The results of experiment demonstrated that in those few monkeys where a recognizable central nucleus does occur its nerve cells are not internuncial, and so cannot constitute an integrative centre. They are lower motor neurones which contribute fibres to the third nerve, and these innervate the Rectus superior and Obliquus inferior, and *not* the Recti mediales, in the monkey.

It must therefore be concluded that the central nucleus of Perlia can in no meaning of the words be considered the "centre for convergence"; nor does it seem likely that any other brain-stem centre, in the topographical sense, could be substituted for this function. In view of these findings, and those of previous workers, little basis remains for further perpetuation of this old and ill-conceived idea.

Acknowledgments

It is a pleasure to acknowledge my indebtedness to Professor G. A. G. Mitchell for the generous facilities of his department, and to Mr. Philip Howarth for his skilful help in photography. The diagrams are by Miss Mary Taylor.

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LEGENDS TO PLATES

PLATE IX

FIG. 2.—Transverse section of monkey's oculomotor complex in its lower (caudal) third, showing the caudal central nucleus (C.C.N.). Cresyl fast violet. × 30.

FIG. 3.—Transverse section at upper (cranial) limit of monkey's oculomotor complex, which is represented at this level only by the antero-median nucleus (parasympathetic component). Cresyl fast violet. × 30.

FIG. 4.—Typical transverse field at intermediate levels of oculomotor mass in the monkey. Note loose paramedian groups of cells (P.M.) near mid-line and absence of central nucleus of Perlia. Cresyl fast violet. × 30.

FIG. 5.—Transverse section through monkey's oculomotor nuclei showing ventrally a central nucleus of Perlia (P.). The dorsal median mass (E.-W.) consists of the Edinger-Westphal columns, joining to form the antero-median nucleus. Cresyl fast violet. × 30.

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PLATE X

FIG. 6.—Transverse section of chimpanzee's oculomotor complex in its upper (cranial) half. Note breadth of median raphe, poorly developed Perlia's nucleus (P.), Edinger-Westphal columns (E.-W.), and cranial extension of caudal central nucleus (C.C.N.). Cresyl fast violet. × 30.

FIG. 7.—Adult human oculomotor nuclei in transverse section at similar level to figs. 4–6. Perlia's central nucleus (P.) is represented by a few cells in the ventral part of the median raphe. The Edinger-Westphal nuclei (E.-W.) are well-developed. Cresyl fast violet. × 20.

FIG. 8.—Typical multipolar nerve cells of the main (somatic) oculomotor nucleus. Compare with figs. 9 and 10. Monkey. Cresyl fast violet. × 550.

FIG. 9.—Nerve cells of the caudal central nucleus (*v.* fig. 2). Monkey. Cresyl fast violet. × 550.

FIG. 10.—Nerve cells of the antero-median nucleus (*v.* fig. 3). Similar cells form the Edinger-Westphal groups. Monkey. Cresyl fast violet. × 550.

PLATE XI

FIG. 11.—Transverse section of chimpanzee's oculomotor nucleus near its upper (cranial) extremity. Note absence of Perlia's nucleus. Dorsally the Edinger-Westphal columns (E.-W.) are joining together. Cresyl fast violet. × 30.

FIG. 12.—Transverse section of oculomotor complex in a monkey killed 10 days after extirpation of the left Rectus superior. A nucleus of Perlia (P.) is present, and retrograde degeneration has occurred in some of its nerve cells (*v.* fig. 14). Cresyl fast violet. × 30.

FIG. 13.—Part of the field shown in fig. 5, from mid-brain of a monkey subjected to extirpation of right Rectus medialis. Swelling, nuclear eccentricity, and chromatolysis are seen in cells of the *right* oculomotor nucleus but *not* in the adjoining nucleus of Perlia (P.). Cresyl fast violet. × 100.

FIG. 14.—Higher magnification of some of the cells forming the nucleus of Perlia shown in fig. 12. About half of these show the changes characteristic of retrograde degeneration, following extirpation of one *Rectus superior*. Cresyl fast violet. × 150.

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PLATE IX

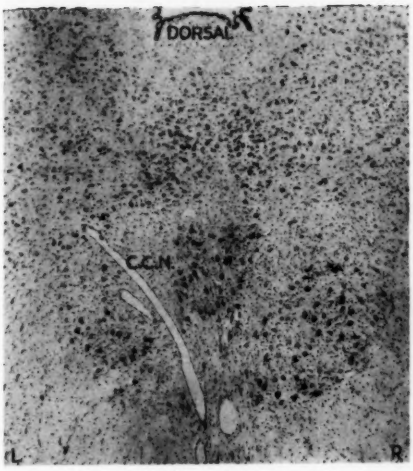
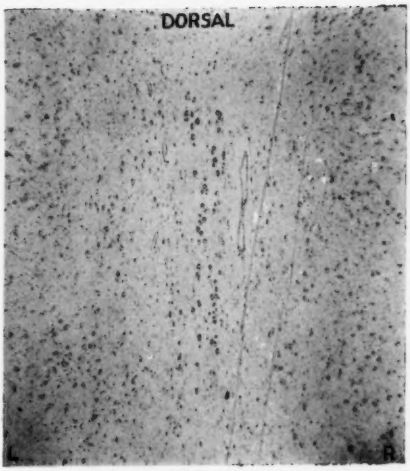


FIG. 2



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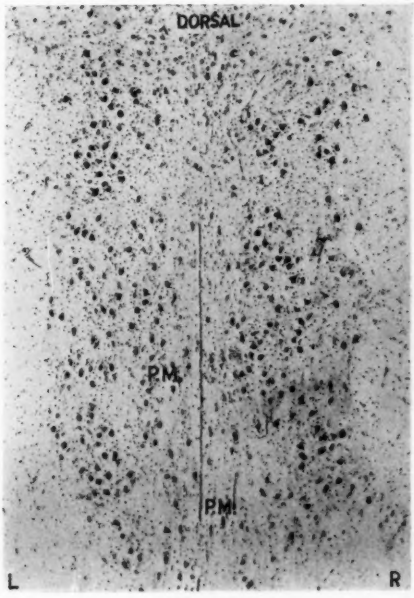

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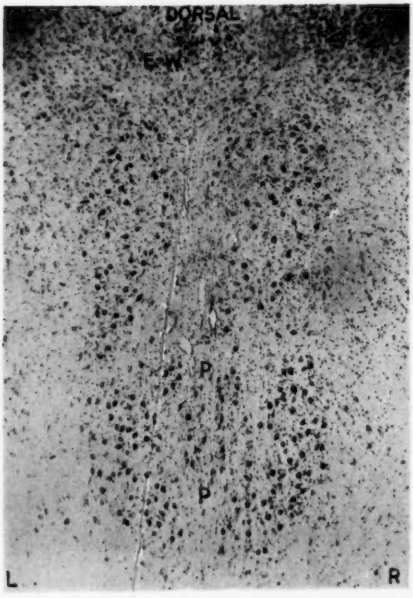

FIG. 5

To illustrate article by Roger Warwick.

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PLATE X

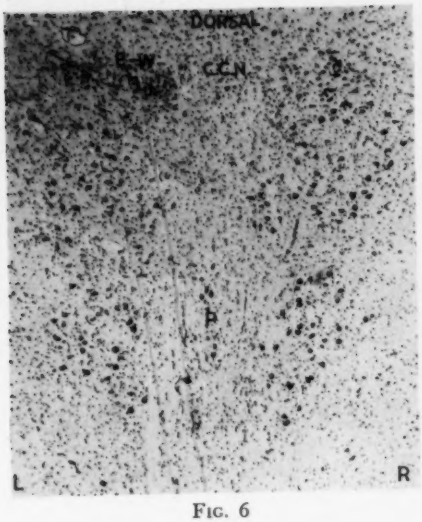
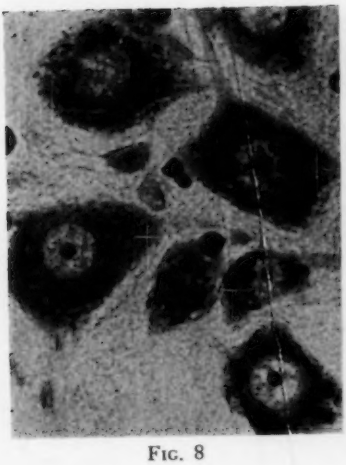


FIG. 6

FIG. 7



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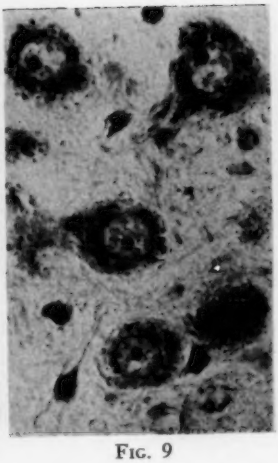

FIG. 9

FIG. 10

To illustrate article by Roger Warwick.

PLATE XI

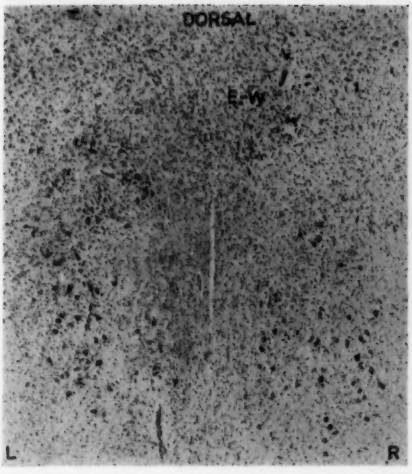

FIG. 11

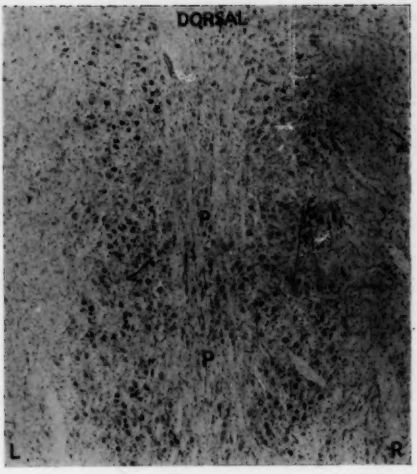

FIG. 12

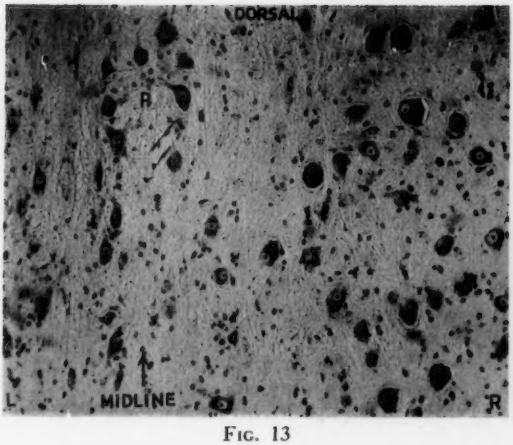

FIG. 13

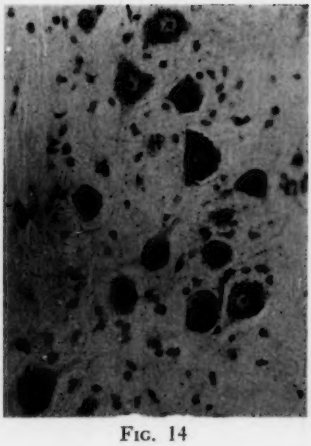

FIG. 14

To illustrate article by Roger Warwick.

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AN EXPERIMENTAL STUDY OF THE EFFERENT CONNEXIONS OF THE HIPPOCAMPUS

BY

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Department of Anatomy, University of Oxford

Introduction

In recent years several important papers on the extrinsic connexions of the hippocampus have appeared (Gerebtzoff, 1941; Allen, 1944; Sprague and Meyer, 1950; Simpson, 1952). While there is general agreement concerning the main projection of its efferent fibres, a number of points still remain obscure, for example the composition of the ventral hippocampal commissure, the projection to hypothalamic nuclei other than the medial mamillary nucleus, the question of a topical organization in the projection of the various hippocampal fields to the hypothalamus and septum, and the possibility of species differences. Some light has been thrown on these problems by the present investigation, in which the loss of fibres following lesions of the hippocampus-fornix system has been studied in activated protargol (Bodian, 1936) preparations. Although this technique has not previously been used in the study of this system, it may be expected to give positive results provided the degeneration is sufficiently well marked and consistent. Our results extend a previous study on the retrograde cell degeneration following lesions of the fimbria (Daitz and Powell, 1954).

Thirty-two rats, ten rabbits and two macaque monkeys were used in this study. The rats varied in age from four days to mature adults and were allowed to survive for periods ranging from one to ten months after operation. Lesions of the hippocampus-fornix system were made by inserting a fine ophthalmic knife or a glass-insulated electrode through a trephine hole in the skull to a suitable depth as estimated from preliminary studies. In all cases the cingulate gyrus and the corpus callosum were severely damaged. The majority of the lesions were unilateral but in four rats bilateral fimbrial section was attempted. The experimental procedure was similar in the rabbits, most of which were adults and were allowed to survive for one to three months. In one monkey the fornix was sectioned by a transcallosal approach; in the other the fimbria was divided as it

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curves up from the inferior horn of the lateral ventricle (i.e. behind the hippocampal commissure). The monkeys were killed seven and ten weeks respectively after operation.

The brains were fixed in 70 per cent alcohol and 2 per cent acetic acid or in the alcohol-formalin-acetic acid mixture of Bodian (1937). In each case blocks containing the septum, thalamus, hypothalamus, amygdala and hippocampus of both sides were embedded in paraffin wax and sectioned coronally at 15 or 25μ.

Results

Rats

As most of the observations have been made on the rat material this will be presented first, and as many of the lesions were similar only a few representative experiments will be described.

Complete division of the fimbria and dorsal fornix.—In experiment H57 the fimbria had been completely interrupted at the anterior end of the hippocampus and the overlying callosal fibres and cingulum were damaged locally. The rostral part of the hippocampus itself had been almost completely destroyed, the lesion extending medially to the mid-line and dividing the fibres of the dorsal fornix of this side. The anterior nuclei of the thalamus, together with the stria terminalis, were directly involved; the stria habenularis remained intact (text fig. 1).

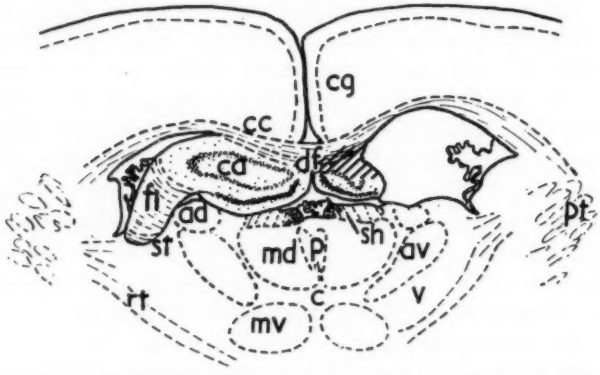

Fig. 1.—Diagram showing the extent of the lesion in experiment H57.

A convenient starting point for the description of the fibre loss is the ventral hippocampal commissure at the level of the interventricular foramen immediately rostral to the lesion. On the affected side the commissure shows marked fibre loss. The lateral half, which is directly continuous with the fimbria posteriorly, is completely devoid of fibres throughout its

entire antero-posterior extent. Posteriorly, the medial half is also completely devoid of fibres, but more anteriorly an increasing number of transversely running fibres, continuous with those of the opposite side, appear. These fibres can be traced laterally to the junction of the medial and lateral halves of the commissure where they appear to stop abruptly. Similar transversely running fibres are, however, seen in every section as far forwards as the septum. The appearance of these fibres is paralleled by a corresponding decrease in the number of fibres on the normal side (Plate XII, fig. 1). As no definite group of transversely or obliquely cut fibres can be seen either anterior or posterior to this level, there is no indication whether these fibres turn forwards into the septum or back towards the fimbria. The longitudinally running fibres of the dorsal fornix which normally lie dorsal to the transverse fibres of the commissure are also completely absent on this side.

In the septum the majority of the pre-commissural fibres have disappeared on the affected side. Posteriorly a few scattered fasciculi having a dorso-lateral orientation—the direction of the fimbrial fibres—are still to be seen in the region of the lateral septal nucleus (Plate XII, fig. 2). There is a small bundle of vertically disposed fibres directly continuous with the anterior pillar, close to the mid-line; this is reduced to approximately a third of the width of the normal bundle on the opposite side and is only seen in the ventral third of the septum. Further anteriorly there are no remaining fibres at all on the operated side (Plate XII, fig. 3).

On the normal side the fimbrial fibres can be traced from the level of the ventral hippocampal commissure forwards and downwards behind the anterior commissure as the anterior pillar of the fornix before turning backwards into the hypothalamus in the descending column. The descending column crosses the medial aspect of the stria habenularis and is in such intimate relationship to it that it is not at all clear whether there is any interchange of fibres between these tracts. On the operated side the anterior pillar, although reduced to about one-third the size of the normal, is still present; the medial cortico-habenular tract, placed immediately lateral to the pillar, is apparently unaffected. The persisting fibres in the anterior pillar and descending column can be traced back for a short distance until the latter crosses the stria habenularis (Plate XII, fig. 4): the exact destination of these remaining fibres cannot be determined, but as they cannot be traced beyond this point they probably end either by joining the stria habenularis or by ending in the region of the paratænial nucleus of the thalamus or in the subjacent anterior hypothalamic area.

The medial cortico-hypothalamic tract (Gurdjian, 1927) can be seen on the normal side as a group of distinct fasciculi arising from the dorsal

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aspect of the descending column at the level at which the latter crosses the stria habenularis. These fasciculi then turn down along the medial aspect of the column and descend vertically in the periventricular area towards the optic chiasma. They fan out in an antero-posterior direction and can be traced into the anterior hypothalamic area and the supra-chiasmatic nucleus, and possibly reach as far caudally as the ventromedial and dorsomedial hypothalamic nuclei. They can be clearly distinguished from a wider group of similar fibres situated more laterally which can be traced into continuity with the pre-commissural component of the stria terminalis. On the operated side both these groups of fibres have completely disappeared. The descending column posterior to the level of the stria habenularis is also completely devoid of fibres (Plate XIV, fig. 1).

Behind the lesion the fimbria and dorsal fornix have lost all their fibres and have undergone severe gliosis. A similar loss of fibres has occurred in the alveus over all the pyramidal cell fields of the hippocampus; it should be emphasized, however, that no such fibre loss can be seen in the fibre plexus of the stratum oriens and there is no demonstrable change in the hippocampal cells (Daitz and Powell, 1954). Despite the changes in the ventral hippocampal commissure there is no detectable loss of fibres in the intact fimbria and alveus of the opposite side. Immediately behind the lesion the stria terminalis is practically devoid of fibres and severely gliosed, but more caudally, where it arises from the amygdaloid nuclei, it appears to be intact. In front of the lesion all components of the stria terminalis, with the exception of one small fasciculus which joins the anterior commissure, have disappeared.

Unilateral fimbrial section without involvement of the dorsal fornix.—In experiment H50 the lesion differs from that of the previous experiment in that the fimbria and stria terminalis were selectively cut without involvement of the dorsal fornix. This has made it possible to assess the relative contribution of the dorsal fornix to the pre- and post-commissural system of fibres.

The lesion extends from the level of the anterior end of the habenular nuclei to just behind the rostral end of the hippocampus. Posteriorly the lateral part of the hippocampus (fields C.A.2 and C.A.3) have been destroyed together with the fimbria; the extent of the damage gradually decreases anteriorly and ends behind the ventral hippocampal commissure. The overlying cingulate gyrus and the immediately subjacent thalamic nuclei have also been involved. The stria terminalis has been completely divided, but the dorsal fornix and ventral hippocampal commissure have not been encroached upon (text fig. 2).

The appearance of the ventral hippocampal commissure (Plate XIII,

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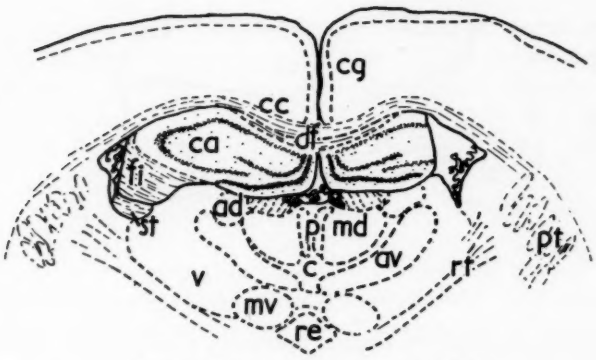

FIG. 2.—Diagram of lesion in rat H50.

fig. 1) and septum is similar to that of experiment H57 except for the presence of the dorsal fornix on both the operated and unoperated sides, and for a band of vertically disposed fibres ventral to this which is reduced to about two-thirds the size of that on the normal side. The anterior pillar on the operated side is reduced to about two-thirds of the diameter of its fellow on the normal side, but the density of the fibres appears to be unchanged. Behind the level of the anterior commissure the fascicles of the medial cortico-hypothalamic tract have disappeared and the descending column of the fornix is reduced to approximately one-half to two-thirds of the normal diameter. At successively more posterior levels the diameters of the descending columns of the two sides gradually approximate, but the diameter of the tract on the unoperated side always remains the larger (Plate XIII, fig. 2). Caudal to the level of the lesion the fimbria has undergone virtually complete fibre loss except for a narrow band of fibres at its base overlying the stratum oriens. The alveus likewise shows a total loss of fibres over fields C.A.2 and C.A.3 but is apparently normal over field C.A.1 (Plate XIII, figs. 3 and 4).

Bilateral fimbrial section (F.S.4).—On the right side the rostral part of the hippocampus and fimbria have been completely destroyed. The lesion, however, does not encroach on the ventral hippocampal commissure, and posteriorly a narrow cut extends as far back as the inferior horn of the lateral ventricle. The lateral part of the dorsal fornix of this side has been slightly damaged. On the left side the lesion is somewhat more restricted, the fimbria and lateral two-thirds of the hippocampus being completely destroyed without involvement of the dorsal fornix or the ventral hippocampal commissure. The stria terminalis is completely severed on the right side but only slightly damaged on the left side (text fig. 3).

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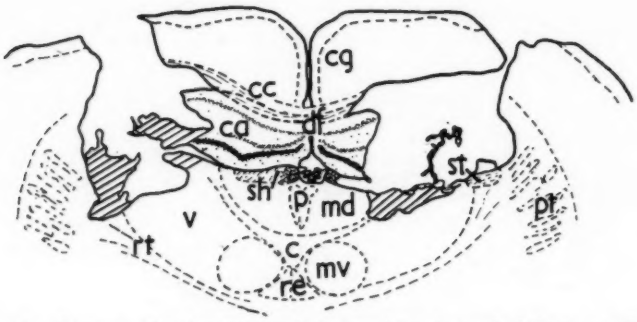

FIG. 3.—Diagram showing bilateral destruction of the fimbria in rat F.S.4.

Rostral to the lesion the remaining portion of the fimbria of both sides and the ventral hippocampal commissure show almost total fibre loss; the few fibres that remain in the commissure can, in most cases, be traced into continuity with the cells of the bed nucleus of the commissure and those of the septo-fimbrial nucleus. In the posterior part of the septum the lateral half of the lateral septal nucleus shows a complete loss of fibres and only very few with a dorsolateral orientation persist in the medial half of this nucleus. The vertically disposed column of fibres, adjacent to the mid-line shows little difference on the two sides at this level, although compared with a normal preparation both sides are reduced by about one-third (c.f. experiment H50). Further anteriorly the lateral septal nucleus is completely devoid of fibres and the vertical column of fibres close to the mid-line is slightly smaller on the right side than on the left, the loss of fibres having occurred mainly from its lateral part. Both the anterior pillars and the succeeding descending columns are of the same diameter. In the absence of a "control" side, however, it is difficult to assess the degree of fibre loss which has occurred, but this appears to be of the same order as in experiment H50. The descending columns decrease progressively as they are traced downwards; nevertheless quite a compact bundle of fibres reaches the mamillary nuclei on each side. The medial cortico-hypothalamic tract has disappeared on both sides. Behind the level of the lesion the fimbriæ of both sides are practically devoid of fibres and, as in H50, this fibre loss extends into the alveus over fields C.A.2. and C.A.3. Fibres which can be traced into the dorsal fornix still remain over field C.A.1.

Bilateral destruction of fimbria and dorsal fornix (*D225*).—The extreme rostral extension of the lesion reaches the junctional region of the ventral hippocampal commissure and the septum; behind this, the posterior half of the ventral hippocampal commissure and the dorsal fornix of both

sides have been completely destroyed. The ventral margin of the fimbria on the left side has not been directly involved but on the right side it has been completely divided. Both striæ terminales have escaped damage. On the left side the lesion stops at the anterior end of the hippocampus itself, but on the right side the lesion extends right through the hippocampus chiefly involving fields C.A.1 and C.A.2.

The remaining portion of the ventral hippocampal commissure is practically devoid of fibres except in its ventral part where a few fibres—in continuity with those of the undamaged portion of the left fimbria—can be traced as far medially as the mid-line, where they appear either to terminate or to turn forwards into the region of the medial septal nucleus; their exact termination, however, cannot be determined with certainty. The septum of both sides shows complete fibre loss except posteriorly where there are a number of fibres present on both sides; these are directed dorsoventrally from the junction of the middle and dorsal thirds of the septum into the anterior pillar. These are in fact the only fibres which are seen in the anterior pillar and even they, like the adjacent intact medial cortico-habenular tracts, cannot be traced in the descending column beyond the level at which this bundle crosses the stria habenularis (cf. H57). Caudal to this level the descending columns have completely atrophied, and the medial cortico-hypothalamic tracts have likewise degenerated. Behind the level of the lesion both fimbriæ show a marked fibre loss. On the left side a few fibres have escaped degeneration in addition to those at the base of the fimbria overlying the stratum oriens. On the right side only the rim of fibres at the base of the fimbria persists, the rest of the fimbria (which at this level has not been directly damaged) showing a total loss of fibres. This severe fibre loss is continued into the alveus of both sides. All components of both striæ terminales are intact.

Unilateral division of the stria terminalis without involvement of the fimbria R7).—In this experiment the primary lesion was placed in the striatum and basal fore-brain areas, but it has incidentally completely divided the stria terminalis of the left side where it curves around the ventral angle of the lateral ventricle. Although the lesion has encroached on the dorsolateral part of the septum of this side the fibres of the precommissural fornix have been only slightly damaged. The fimbria and descending column of the fornix have escaped damage and show no sign of fibre loss. The medial cortico-hypothalmic tract is intact but the fibres of all components of the stria terminalis have completely degenerated. Behind the level of the lesion the stria terminalis shows a total loss of fibres with concomitant gliosis as far back as the inferior horn of the lateral ventricle; however, at the level at which the stria turns up from

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the amygdaloid nuclei there is no apparent loss of fibres and the bundle appears to be unchanged.

Destruction of dorsal fornix and septum.—In experiment R30 the whole of the rostral part of the septum of the right side has been destroyed together with the fibres of the dorsal fornix as they turn down to join the anterior pillar of the fornix; the lateral extension of the lesion interrupts the stria terminalis but the anterior pillar and descending column of the fornix have escaped direct damage. The only change in the region of the ventral hippocampal commissure is a severe fibre loss in the lateral two-thirds or more of the dorsal fornix of the right side. The anterior pillar of this side is reduced to approximately one-half of the normal diameter, but the medial cortico-habenular tract is apparently unchanged. Posterior to the level at which the fornix crosses the stria habenularis the descending column undergoes a very rapid reduction in diameter and has virtually disappeared at the level of the posterior end of the suprachiasmatic nucleus. At the most, only a very small fraction of fibres can be traced back to the level of the mamillary nuclei; and these may well be derived from that small portion of the dorsal fornix which was not involved by the lesion. Despite the obvious damage to fibres of the fimbria which project to the septum, there is no evidence of retrograde fibre loss in either the fimbria or alveus.

Destruction of septum and descending column of fornix.—The lesion in experiment R6 has destroyed the entire septum of the left side as far back as the level of the ventral hippocampal commissure, and by a ventral extension into the hypothalamus it has completely interrupted the descending column together with the medial cortico-hypothalamic tract and the stria terminalis of this side. Behind the level of the lesion, the descending column of the fornix is completely atrophied. However, there is no retrograde fibre degeneration in either the ventral hippocampal commissure, the fimbria, the alveus, the dorsal fornix or the stria terminalis.

Rabbits

As many of the lesions in these animals are similar and resemble those previously described in the rats, only four experiments will be described, emphasis being laid on those features which differ in the two species.

Destruction of dorsal fornix hippocampus and fimbria.—In rabbit 8 the hippocampus of the left side has been severely damaged throughout its antero-posterior extent and the fimbria almost completely divided just behind the ventral hippocampal commissure, only a few fibres remaining in its dorsal part. The dorsal fornix of this side has also been completely interrupted, with possible marginal involvement of the opposite side (text

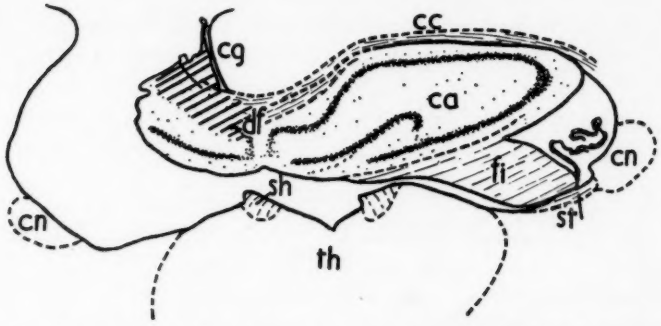

FIG. 4.—Destruction of hippocampus, dorsal fornix and fimbria in rabbit 8.

fig. 4). The ventral hippocampal commissure shows surprisingly little change and well-defined fasciculi can be seen extending across its entire width; only in the immediate vicinity of the lesion is there any appreciable loss of fibres.

There is a marked reduction in the number of fibres in the region of the lateral septal nucleus, which becomes more severe anteriorly; in the posterior part of the septum, however, there remain a number of fasciculi with a dorsolateral orientation. The vertical column of fibres adjacent to the mid-line, and continuous above with the dorsal fornix, is almost completely atrophied.

On the normal side the anterior pillar is seen as a well-defined bundle passing backwards and downwards behind the anterior commissure close to the ependyma of the third ventricle and comes into an even more intimate relationship with the stria habenularis than is seen in the rat. At this level, in some preparations, a few rather ill-defined fasciculi can be seen apparently leaving the dorsomedial aspect of the descending column and passing downwards in the periventricular area towards the anterior hypothalamic area. These fasciculi are very much smaller and more restricted in their antero-posterior extent than the homologous medial cortico-hypothalamic tract as described in the rat. That a considerable number of fibres, however, are given off in this area is indicated by the sudden reduction in diameter of the descending column consistently seen at this level. On the operated side the gliosis which has replaced the vertical column of fibres in the septum can be traced into the similarly degenerated medial two-thirds of the anterior pillar. After passing behind the anterior commissure the descending column is even further reduced so that at caudal levels very few fibres remain; the fibres of the medial cortico-hypothalamic tract have also disappeared. The fimbria and alveus caudal to the lesion show no apparent loss of fibres.

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Unilateral fimbrial section.—In rabbit 42 a well-circumscribed electrolytic lesion was placed in the fimbria of the left side immediately behind the ventral hippocampal commissure. The fimbria had been completely divided with minimal damage to the overlying hippocampus; the dorsal fornix remained intact (text fig. 5). Again there does not appear to be

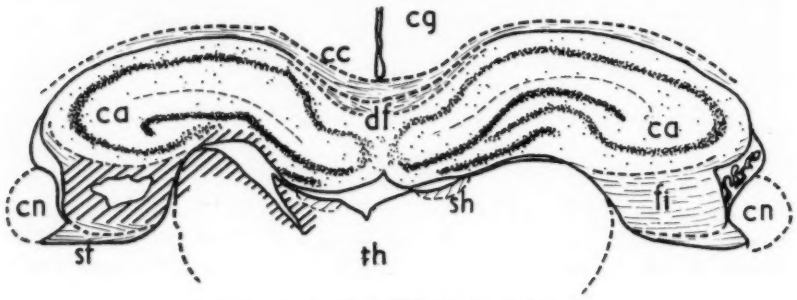

FIG. 5.—Lesion in the fimbria in rabbit 42.

any significant loss of fibres in the ventral hippocampal commissure. Unfortunately the sections of the septum in this experiment are poorly impregnated and only the medial vertical column of fibres continuous with those of the dorsal fornix can be distinguished. The anterior pillar on the operated side is reduced to approximately two-thirds the diameter of its fellow. Immediately behind the level of crossing of the stria habenularis the difference in diameter between the two descending columns is dramatically reduced so that by the level at which the ventromedial hypothalamic nuclei are reached the diameter of the column on the operated side is not less than four-fifths of that of the normal side (Plate XIV, fig. 2). Although both columns are progressively reduced posteriorly, the difference in diameter between the two remains more or less constant and the fibre density is apparently the same on both sides. No evidence concerning the origin of the fibres of the medial cortico-hypothalamic tract could be obtained from this experiment as no definite fasciculi were seen arising from the descending column of the normal side. No significant retrograde fibre loss is seen in the fimbria and alveus behind the lesion.

Unilateral destruction of the dorsal fornix (R36).—In this experiment the lesion had completely destroyed the dorsal fornix of the left side together with the overlying cingular gyrus. The left hippocampus itself, although distorted by the resultant hydrocephalus, had not suffered much damage and the fimbria is intact. The dorsal fornix and the rest of the hippocampal-fornix system of the right side are undamaged.

The hippocampal commissure shows no change, but in the septum the vertical column of fibres adjacent to the mid-line and continuous with the dorsal fornix above has completely degenerated. There is no diminution in the number of fibres in the lateral septal nucleus.

The anterior pillar is reduced in diameter to about one-half that on the normal side, but just behind the level of the interventricular foramen the fascicles of the medial cortico-hypothalamic tract can be seen leaving the descending column on both sides (Plate XIV, fig. 3). Although both descending columns normally undergo a reduction in size at this level, the relative size of the two columns remains more or less constant throughout the hypothalamus, and the difference between them is accentuated as the mamillary nuclei are approached (Plate XIV, fig. 4).

Destruction of the descending column.—In rabbit 45 the ventral three-quarters or more of the descending column had been destroyed by an electrolytic lesion placed just behind the anterior commissure. Only a very small proportion of fibres remain in the descending column behind the lesion. Above the lesion, however, the fibres show no retrograde change either in the anterior pillar, hippocampal commissure, dorsal fornix, fimbria or alveus.

Monkeys

Unilateral fimbrial section.—In M.H.2 the fimbria was divided at the level where it adjoins the ventral hippocampal commissure and the latter had also been damaged in its lateral half. Most of the fimbria and alveus and part of the hippocampus of this side have undergone a necrosis as a result of interference with their vascular supply from the choroid plexus. The remaining portion of the hippocampal commissure shows no appreciable loss of fibres, nor is there any evidence of a thinning out of fibres of the opposite side. The subcallosal fornix has undergone practically complete fibre loss. Anteriorly, at the level of the subfornical organ, however, there is a distinct, transversely running bundle of fibres along the ventral margin of the adjacent fornix columns (Plate XIV, fig. 5). This bundle is continued into the opposite side and, although it only occupies an anteroposterior extent of some 0·8 to 1·0 mm., it is quite sharply defined both anteriorly and posteriorly. Apart from the intrinsic fibre plexus, the septum of the operated side shows an almost complete loss of fibres. The anterior pillar is likewise degenerated and gliosed. At the anterior end of the thalamus a few distinct fascicles can be seen leaving the medial margin of the descending column of the normal side and running ventrally alongside the ependyma of the third ventricle towards the anterior hypothalamic area. These fibres (which correspond to the medial cortico-

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hypothalamic tract of the rat) have atrophied on the operated side (Plate XIV, fig. 6). The remainder of the descending column has completely degenerated and is devoid of fibres throughout its entire course in the hypothalamus.

Transcallosal division of fornix.—In this experiment, M.H.1, the right fornix had been completely divided beneath the corpus callosum in front of the ventral hippocampal commissure. The medial edge of the fornix of the opposite side had been slightly involved by the lesion and the anterior nuclei of the thalamus were also directly damaged. As protargol-stained preparations of the septum are not available it has not been possible to assess the changes in the precommissural system of fibres. The descending column, however, is completely degenerated. Caudal to the lesion of the fornix the hippocampal commissure, fimbria and alveus show no sign of retrograde fibre degeneration.

Discussion

From the description of the results it will be noted that each component of the hippocampal-fornix system has been selectively damaged in one or other of the experiments. For the sake of convenience each component will be discussed separately.

Perhaps one of the most interesting observations is the almost total loss of fibres which occurs in the fimbria and dorsal fornix behind the level of the lesion on the operated side in the rats following interruption of these tracts. A proportion of this fibre loss may be attributed to the antegrade degeneration of the caudally directed fibres in the fimbria which have been described by Morin (1950), Ajmone-Marsan and Stoll (1951) and Daitz and Powell (1954). In addition to these fibres (which arise from the medial septal nucleus), account should also be taken of the caudally directed commissural fibres from the fimbria of the opposite side. However, these two components probably constitute only a small percentage of the total number of fibres in the fimbria and the evidence strongly suggests that, in the rat at least, following section of the fimbria or dorsal fornix, retrograde fibre degeneration may occur in the fimbria and alveus. That the retrograde changes which occur in these fibre paths is a genuine fibre degeneration, and not the result of vascular impairment, is indicated by the following observations: (*a*) the histological appearance of the fimbria and alveus is not at all indicative of necrosis, the outline of the fimbria being well preserved with no gross disintegration or cellular infiltration; (*b*) apart from the alveus no layer in the hippocampus shows any evidence of degeneration (either of fibres or cells), and fine normal fibres are frequently seen at the base of the fimbria even when the rest

of the fimbria and alveus are totally degenerated; (*c*) following selective division of the fimbria or dorsal fornix the fibre loss in the alveus is always restricted to certain of the pyramidal cell fields only and there is no reason to suppose that vascular interference would be regionally limited in this way. However, since retrograde changes were not seen after lesions of the anterior pillar and descending column in the rat, or after section of the fimbria in the rabbit, while in the monkey M.H.2 quite obvious vascular necrosis occurred after cutting the fimbria with incidental involvement of the choroid plexus, it must be emphasized that impairment of the vascular supply cannot definitely be excluded. The necrosis in the monkey, however, was in striking contrast to the degeneration seen in the rat since it extended well into the hippocampus itself and was accompanied by much cellular degeneration.

Alveus.—It has been shown that after section of the fimbria in the rat retrograde fibre degeneration occurs in the alveus over fields C.A.2 and C.A.3, whereas degeneration over field C.A.1 occurs when the dorsal fornix is involved. The conclusion that the fibres of the dorsal fornix are derived from field C.A.1 and those of the fimbria from C.A.2 and C.A.3 is substantiated by the orientation of these fibres in the alveus over these fields as seen in normal Bodian and Golgi-Cox preparations. In these the axons of the pyramidal cells of field C.A.1 can be seen to turn medially in the alveus into the dorsal fornix while these of cells in fields C.A.2 and C.A.3 bend laterally towards the fimbria. The junction between fields C.A.1 and C.A.2 is in fact clearly indicated by the divergence in direction of the fibres in the overlying alveus. This observation provides the first definite indication of a topical organization in the efferent projection of the hippocampal fields and may be correlated with the known differences in the afferent connexions of these fields and with the differences in the projection of the fimbria and dorsal fornix to the nuclei of the hypothalamus. The main afferents of field C.A.1 are derived from the medial part of the entorhinal cortex by way of the temporo-alvear pathway, while those to the remaining hippocampal fields arise in the lateral part of the entorhinal cortex and reach the hippocampus by the perforating tract of Cajal (Cajal, 1911; Lorente de Nó, 1934; Adey and Meyer, 1952). In the interpretation of our observations, however, two other findings should be re-emphasized, namely that retrograde fibre loss did not occur in the alveus after lesions of the anterior pillar or descending column, and that such degeneration did not occur in either the rabbit or the monkey.

The fimbria and the hippocampal commissure.—After section of the fimbria in the rat the only fibres remaining behind the lesion form a

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narrow rim at the base of the fimbria. Since they persist on both sides, even after bilateral fimbrial section, it is probable that they represent intra-hippocampal association fibres. That the caudally directed fibres from the medial septal nucleus and the commissural fibres from the hippocampus of the opposite side form only a small proportion of the total fibres of the fimbria in both the rat and rabbit, is evidenced by the fact that no marked fibre loss occurs in the fimbria either after lesions of the septum, or, on the unoperated side, after unilateral section of the fimbria. In all animals no fibres persisted in the fimbria rostral to the lesion when it was completely divided.

Changes in the ventral commissure were only found in the rat experiments. After a bilateral section there is complete fibre loss in the commissure, while after unilateral section there is a marked loss of fibres on the operated side of the commissure but only a slight loss in the normal half. The few fibres that persist on the operated side of the commissure come across the mid-line but cannot be traced beyond the junction of the medial and lateral halves of the commissure. Since Sprague and Meyer (1950) found no evidence in the rabbit of a contralateral projection of the fornix to the septum or the hypothalamus anterior to the mamillary nuclei the exact distribution of these fibres is uncertain. The absence of retrograde fibre change in the commissure or fimbria after lesions of the septum, anterior pillar or descending column may possibly be explained on the basis of collateral branching at the level of the commissure as described by Cajal (1911). The presence, in the monkey, of transverse fibres between the two subcallosal fornices should be mentioned in this connexion, although the exact origin and destination of these fibres are unknown. Since they persist after complete unilateral fimbrial section, the following possibilities must be considered: (a) that they are derived from the fimbria of the opposite side (although on the normal side in monkey M.H.2 there does not appear to be any significant fibre loss, but this, if present, would be slight); (*b*) that they are derived from the cingular gyrus; this is unlikely because the gyrus was destroyed in M.H.2 as far forwards as the central sulcus; (*c*) that they originate in the septum; but, again in M.H.2, there is no evidence of fibres in the subcallosal fornix behind the level of the commissure (as far back as the lesion). This commissure is of interest in view of the bilateral projection from the septum to the tip of the temporal lobe by the fornix reported in the monkey by Ajmone-Marsan and Stoll (1951) and of bilateral terminal degeneration in the ventromedial hypothalamic nuclei after lesions of the hippocampus and fornix of this animal reported by Simpson (1952).

Septum.—The changes in the fibre composition of the septum are

essentially the same in the rat and rabbit. Following lesions of the dorsal fornix, the vertically disposed bundle of fibres adjacent to the mid-line (apparently continuous on the normal side with the dorsal fornix above) undergoes complete degeneration. On the other hand, lesions of the fimbria result in degeneration of all the fibres of the pre-commissural fornix fibres and of those which pass into the lateral part of the anterior pillar. Since a small percentage of fibres remains in the region of the medial septal nucleus and in the anterior pillar after complete destruction of the fimbria and dorsal fornix, it is apparent that the septum itself must contribute a number of fibres to the anterior pillar. This is in agreement with the finding of Marchi degeneration in the descending column after lesions of the septum by Morin (1950). In our experiments, however, it is not possible to trace these fibres in the descending column beyond the level at which it crosses the stria habenularis.

Anterior pillar and descending column of the fornix.—Even after complete bilateral division of the fimbria and dorsal fornix in the rat the anterior pillar does not undergo complete degeneration, a small vertically disposed bundle of fibres remaining on either side of the mid-line. From their direction they appear to originate in the posterior part of the lateral septal nucleus. The fibres of the so-called medial cortico-habenular tract likewise remain unchanged. Both these groups of fibres can only be traced as far back as the level at which the fornix column crosses the stria habenularis. Further, in none of our experiments with varying lesions of the hippocampus and fornix was any appreciable fibre loss noted in the stria habenularis. From these observations it is clear that the medial cortico-habenular tract is not hippocampal in origin, a finding that is in agreement with those of Sprague and Meyer (1950) and Simpson (1952) that no terminal degeneration occurs in the habenular nuclei when the hippocampus or fimbria are damaged.

Essentially the same picture is seen in the rat and rabbit after unilateral lesions of the fimbria and dorsal fornix: the descending column undergoes a marked reduction in diameter just behind the anterior commissure. In the rat this reduction is accounted for to a large extent by the well-defined fascicles of the medial cortico-hypothalamic tract which leave the column at this level. In the rabbit the fascicles of the medial cortico-hypothalamic tract are not as well defined as in the rat, but it is almost certain that relatively as many fibres are given off in this region. It has been shown that in both these animals the fibres of this tract are derived from the fimbria, since they do not degenerate after lesions of the stria terminalis or dorsal fornix. A quantitative estimate of the reduction in the number of fibres in the normal descending column as

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it descends has recently been given by Guillery (1954), who concludes that in the rabbit about half of the total number of fibres of the descending column drop out between the anterior commissure and the mid-tuberal region of the hypothalamus. Sprague and Meyer (1950) found in the rabbit no evidence that hypothalamic nuclei rostral to the mamillary body, with the exception of the perifornical nucleus, receive any contribution from the fornix. However, the reduction in size of the normal descending column is greater than can be accounted for by the degeneration in the perifornical nucleus or by the fascicles of the medial cortico-hypothalamic tract and suggests a somewhat diffuse projection which would be difficult to determine by the method of terminal degeneration. A similar group of fascicles has been described in the monkey and, since they undergo degeneration after a lesion of the fimbria (without involvement of the stria terminalis), they are almost certainly of hippocampal origin. This observation may account for the finding of terminal degeneration in the ventromedial hypothalamic nuclei in Simpson's (1952) experiments. An interesting finding has been the relative contribution of the fimbria and dorsal fornix to the descending column in the rat and rabbit. In the rat by far the greater proportion of the fibres of the fimbria almost certainly end in the hypothalamus rostral to the mamillary nuclei since after unilateral fimbrial section the size of the descending column on the normal side immediately in front of the mamillary nuclei is only slightly larger than that on the operated side. After section of the fimbria in the rabbit the changes in the descending column are essentially the same although the reduction in size on the operated side is relatively less. While the two columns approximate in size during their course through the hypothalamus after fimbrial section the converse is seen after selective interruption of the dorsal fornix, again indicating that not only do a considerable number of fibres fall out in the hypothalamus but also that these are mainly derived from the fimbria. In all the animals complete destruction of the dorsal fornix and fimbria results in total atrophy of the descending column below the level of the stria habenularis.

Summary

(1) The fibre loss after varying lesions in the hippocampus-fornix system has been studied in the rat, rabbit and monkey with the use of protargol preparations.

(2) In the rat lesions of the fimbria or dorsal fornix are followed by extensive retrograde fibre degeneration in the fimbria, and alveus.

(3) Lesions of the fimbria in the rat and rabbit result in complete loss of the pre-commissural fibres in the septum and degeneration of the

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medial cortico-hypothalamic tract, but there is only a slight reduction in diameter of the descending column of the fornix at the level of the mamillary nuclei. It is concluded that most of the efferent fibres of the fimbria end in the hypothalamus anterior to the mamillary nuclei.

(4) Division of the dorsal fornix and fimbria results in complete atrophy of the descending column, and it thus is probable that most of the fibres reaching the mamillary nuclei are derived from dorsal fornix.

We wish to thank Mr. Michael Lindsey for valuable technical assistance.

ABBREVIATIONS

ac	—	anterior commissure.	hc	—	ventral hippocampal commissure.
ad	—	anterodorsal nucleus of thalamus.	md	—	mediodorsal nucleus of thalamus.
al	—	alveus.	mh	—	medial cortico-habenular tract.
ap	—	anterior pillar of fornix.	mt	—	mamillo-thalamic tract.
av	—	anteroventral nucleus of thalamus.	mv	—	medioventral nucleus of thalamus.
c	—	nucleus centralis.	p	—	paratænial nucleus of thalamus.
ch	—	medial cortico-hypothalamic tract.	pt	—	putamen.
ca	—	cornu ammonis.	re	—	nucleus reuniens of thalamus.
cc	—	corpus callosum.	rt	—	reticular nucleus of thalamus.
cg	—	cingulate gyrus.	sh	—	stria habenularis.
cn	—	caudate nucleus.	st	—	stria terminalis.
df	—	dorsal fornix.	th	—	thalamus.
f	—	descending column of fornix.	v	—	ventral nucleus of thalamus.
fi	—	fimbria.			

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LEGENDS TO PLATES

PLATE XII

FIG. 1.—Photomicrograph showing fibre loss at the level of junction of the hippocampal commissure and septum in rat H57. × 24. The arrow indicates the mid-line.

FIG. 2.—Photomicrograph showing fibre loss in the posterior part of the septum and in the anterior pillar of the fornix in rat H57. × 24. The arrow indicates the few remaining fibres in the septum of the affected side.

FIG. 3.—Photomicrograph showing complete fibre loss in the anterior part of the septum on the operated side in rat H57. × 24. In this figure the operated side appears on the right.

FIG. 4.—Photomicrograph showing complete loss of fibres in the descending column of the fornix at the level of the stria habenularis in rat H57. × 24. The right and left arrows indicate the medial cortico-hypothalamic tract and the dispersing fibres of the medial cortico-habenular tract respectively.

PLATE XIII

FIG. 1.—The ventral hippocampal commissure and the anterior pillar of the fornix in rat H50. × 24. The arrow indicates the junction of the lateral and medial halves of the commissure on the affected side.

FIG. 2.—Photomicrograph showing the descending columns of the fornix immediately in front of the mamillary nuclei in rat H50 (unilateral fimbrial section). × 24.

FIGS. 3 AND 4.—Photomicrographs of the alveus and fimbria on the normal and operated sides respectively in rat H50. × 46.

PLATE XIV

FIG. 1.—Complete atrophy of the descending column of the fornix on the operated side in rat H57 following destruction of the fimbria and dorsal fornix. × 24.

FIG. 2.—The descending column of the fornix immediately in front of the mamillary nuclei in rabbit 42 following unilateral fimbrial division. × 24.

FIG. 3.—The descending column of the fornix at the level of the interventricular foramen and medial cortico-hypothalamic tracts in rabbit 36. × 24.

FIG. 4.—The descending column of the fornix immediately in front of the mamillary nuclei in rabbit 36 following interruption of the dorsal fornix. × 24.

FIG. 5.—The subcallosal fornix in monkey M.H.2. The arrow indicates the commissural fibres described in the text. × 24.

FIG. 6.—The descending column of the fornix and the medial cortico-hypothalamic tract in monkey M.H.2.

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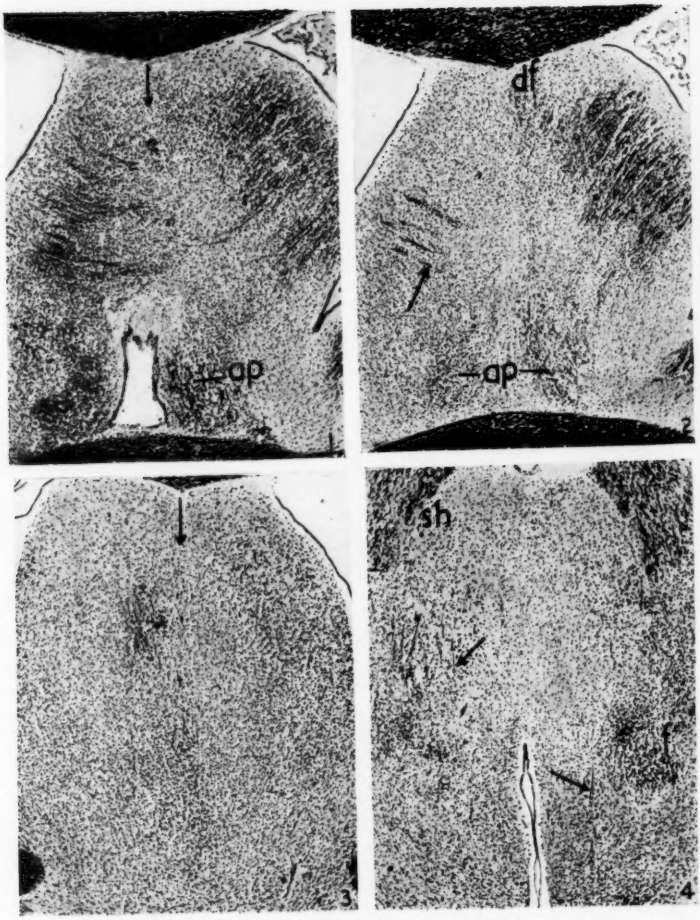

To illustrate article by T. P. S. Powell and W. M. Cowan.

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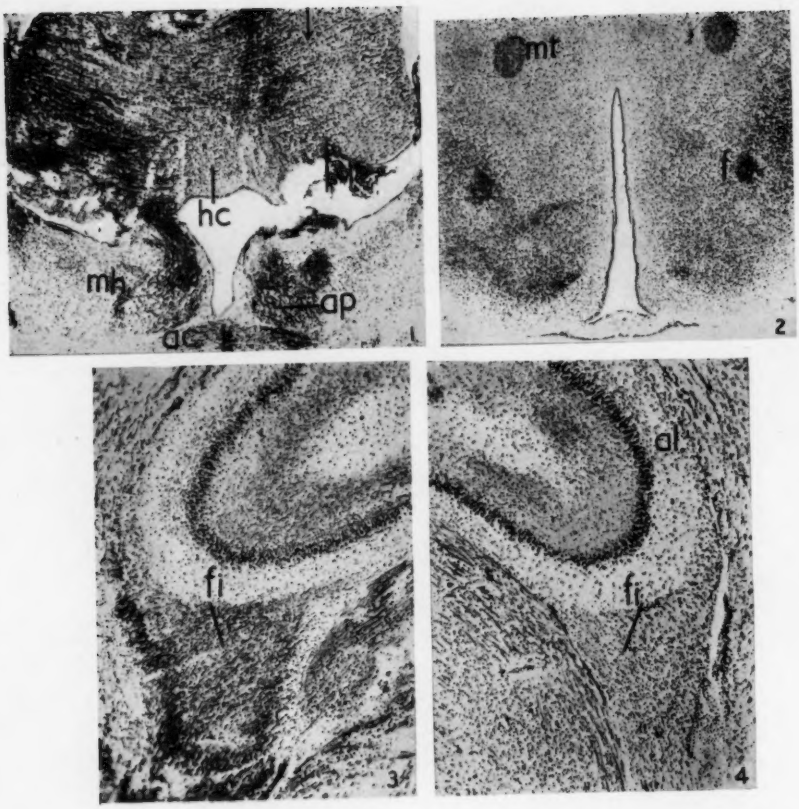

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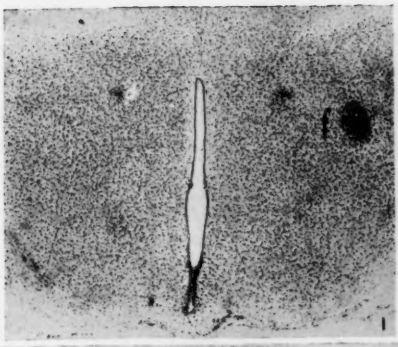
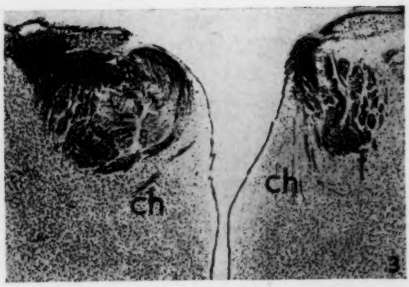
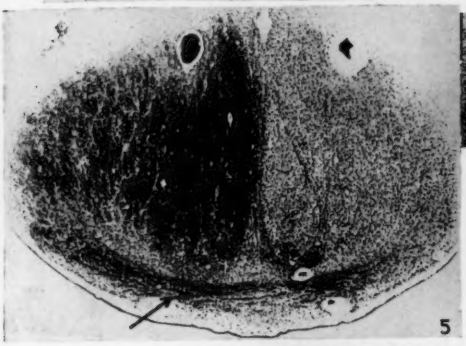
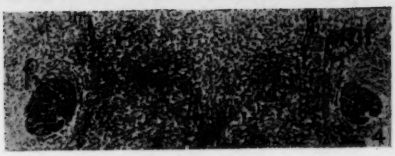
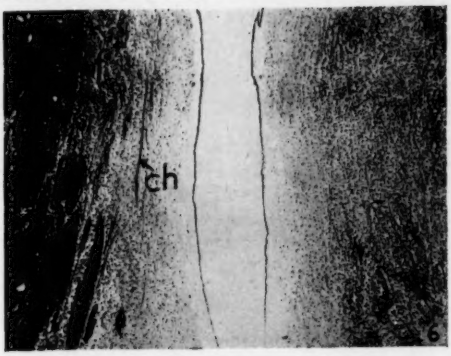
PLATE XIV











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CORTICAL AND SUBCORTICAL SYSTEMS INHIBITING THE KNEE JERK IN THE CAT

BY

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INTRODUCTION

MUCH work recently and in past years has been devoted to the study of inhibition resulting from electrical stimulation of certain regions of the central nervous system (Hecaen, David, and Talairach, 1947; Hines, 1937; McCulloch, Graf, and Magoun, 1946; Tower, 1935). Inhibition of four types has been described; of postural tone, of movements induced at a superior level, of tendon reflexes, and of cortical electrical activity. The early experimental work of Tower (1936) on the extrapyramidal functions of the cat brain has since been elaborated both in animals by Dusser de Barenne and McCulloch (1941) and in man by Garol and Bucy (1944); and by means of the Horsley-Clarke technique, the bulbar reticular formation (Magoun, 1944; Magoun and Rhines, 1946; Magoun and Rhines, 1947) and forebrain (Hodes, Peacock, and Heath, 1951) explored in regard to inhibition of movements.

The connexion between inhibition of muscle tone and initiation of movement was examined by Tower in 1935 by unilateral division of the pyramidal tract in the medulla. She concluded that there is "a pre-spinal dissociation, in large part at least, of the two elements of cortical function." Experiments in the present study were designed, therefore, to trace inhibitory pathways from the cerebral cortex to the pons and to study the relationship of inhibition and movement. In addition, interest in the

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surgical treatment of diseases of the "extra-pyramidal" system directed our attention particularly to the basal ganglia and their efferent pathways.

Bilateral repetitive elicitation of the knee-jerk was used as the background activity for study of the inhibitory systems. This was chosen because of its simplicity and consistency; because comparable bilateral activity is more readily obtainable than by cortical stimulation; because it does not introduce another electrical circuit into the experiment and because it could possibly be correlated with clinical observation. It is a disadvantage that except for the knees the hind limbs are completely immobilized, but spontaneous movements in the rest of the body are not restricted. Variations of muscle tone, followed either by observation of posture against gravity or by electromyography, are an informative and less artificial background but introduce complications.

Methods

Material

Fifty adult cats, ranging in weight between 2·5 and 3·5 kg, were used. Forty-three normal animals were the subjects of acute experiments. Two cats were prepared by unilateral chronic sensorimotor decortication and were subsequently used in acute experiments; one after an interval of four months, the other after four weeks. Two chronic bilateral decorticate animals survived for later experimentation. In each case one side was operated on two months and the other side one month before the acute experiment.

Three animals were used in a supplementary study on the effects of anæsthesia on the inhibitory systems, employing the monosynaptic response recorded oscillographically.

Technique

Anæsthesia: A moderately deep level of anæsthesia was employed. Intraperitoneal nembutal (60 milligrams per kg.) was injected initially, but this was usually the minimum dose required and additional small amounts were often necessary during the experiment. Although tracheotomy and endotracheal intubation were routine, it was rarely necessary to resort to artificial respiration; but this was promptly applied if the respirations were at all depressed. The mechanisms concerned appear to be unusually sensitive to anoxia. On the other hand, too light anæsthesia, when the animal makes movements in response to painful stimuli, results in great variability of the knee-jerk record and base line and in bizarre and erratic responses. The corneal reflexes were usually depressed but obtainable; the pupils were about half dilated.

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After tracheotomy and introduction of an endotracheal tube, the anæsthetized animals were placed in the Horsley-Clarke instrument. Firm fixation to the framework of the instrument was effected by two metal clamps attached to a thoracic and a lumbar spinous process. Pins driven through the lower ends of the femurs immobilized the hips and femurs so that only the lower leg was movable around the fixed axis of the knee. Mechanical elicitation of the deep tendon reflex at the knees was obtained bilaterally at four-second intervals by pivoted strikers activated by cams powered by small electric motors. The amplitude of excursion of the legs was recorded by mechanical transmission to a kymograph. This apparatus is a modification of the one described by Hodes *et al.* (1951).

As small a portion of the calvarium as was necessary was removed and the dura was opened only sufficiently to allow changes in position of the electrode, unless areas of cortex were being explored or excised. The exposed cortex was protected by application of warm mineral oil. The decortications, both acute and chronic, consisted of excision of excitable sensorimotor cortex of the pericruciate area, including the medial portion of the sigmoid gyri. Section of the pes pedunculi was made in seven acute experiments in addition to the usual technique of stimulation. The incision, of about 2 mm. depth, was made high in the peduncle under direct vision by elevation of the temporal lobe.

Stimulation was by concentric bipolar steel electrodes, 1 mm. diameter, guided by the Horsley-Clarke instrument. Electrodes with 2 mm. ball tips were used for cortical stimulation. The most favourable type of electrical stimulus was found to be 60 cycle alternating current from 1 to 3 volts. Square-wave stimuli at frequencies ranging from 30 to 600 per second were investigated but were less effective and required higher voltages—from 5 to 7 volts. The minimum voltage capable of producing a sufficient response only in the most sensitive regions was always used; in fact, great specificity of inhibitory response was obtainable, varying sharply from millimetre to millimetre in most instances.

Anatomical control was achieved by macroscopic and microscopic examination of the brains, which were preserved by intra-arterial formalin perfusion at the end of each experiment.

When a steady knee-jerk record, approximately equal on the two sides, was obtained, stimulation of the area under investigation proceeded. The position of the stimulating electrode was changed by millimetre intervals and each point was stimulated for 10 to 15 seconds at the higher range of intensity. This was reduced as more responsive areas were encountered. The occurrence of inhibition or facilitation of the knee-jerk or of associated movements was noted in terms of the Horsley-Clarke co-ordinates of

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stimulation. At the end of the experiment these points were correlated with the relevant changes in the record and were charted on greatly enlarged tracings of the cat brain. These represented the anatomical structures of the cat brain in 1 mm. sections in the frontal plane of the Horsley-Clarke instrument based on the work of Gerard, Marshall and Saul (1936). The plotting of points of stimulation was subsequently checked and corrected by comparison with the histological sections of the brain. The use of Horsley-Clarke co-ordinates in the text has therefore been largely eliminated, except at certain crucial points.

Results

(*1*) *Location of Inhibitory Areas*

In view of the previous detailed analyses of cortical inhibition, exploration of the cortex in this work was restricted to the identification of an area, stimulation of which consistently inhibits the contralateral knee-jerk. This small area, no more than 3 to 4 mm. in diameter, was located by moving the electrode small distances in an area high on the lateral aspect of the hemisphere just posterior to the cruciate sulcus in the sigmoid gyrus (Ochs, 1954). It was not identically situated in relation to the sulcus from animal to animal.

In the neighbourhood of the head of the caudate nucleus, comprising its lateral half and a small region lateral to this (A 15; L 6; 0 to +5), there is an area of inhibition rather extended in the vertical plane, which becomes more concentrated when followed caudally.

In the posterior limb of the internal capsule (A 10; L 5 to L 8; +2 to −3) the inhibitory structures occupy a medial position, encroaching upon the thalamus at the nucleus ventralis pars anterior, pars arcuata and pars externa. There is no effect from stimulation of the lateral part of the internal capsule, nor from the nucleus lenticularis, but the nucleus entopeduncularis appears to be included in the active zone.

More caudally, the pes pedunculi gives little inhibition. Possibly the diffusion of fibres in the peduncle in contrast to the compact arrangement in the capsule is responsible for this difference in effect. Inhibition is easily obtained from the tegmental area of the mid-brain, from Fields H_1 and H_2 of Forel and from the zona incerta (A 8; L 2 to L 5; +2 to −5). In the tegmental area of the pons, inhibition is readily obtainable from the red nucleus and from the neighbouring reticular formation (A 4; L 3; −3).

Inhibition is always obtained in a region extending from the posterior limb of the internal capsule to the pontine tegmentum; but it is not so readily achieved by stimulation at more anterior levels.

(2) *Characteristics of Inhibition*

With the mechanical method of recording employed in these experiments, there is no appreciable delay in the commencement and ending of the period of inhibition, in relation to the stimulus.

From the cortex to the pre-rubral field, inhibition is strictly contralateral. In the pre-rubral field, inhibition is obtained bilaterally, but as stimulation progresses caudally it becomes ipsilateral in effect, suggesting the occurrence at this level of a somewhat elongated decussation of the fibres mediating inhibition fig. 1A). At the commencement of this region of decussation ipsilateral and bilateral inhibition result from stimulation in the central portion of the mid-brain, from the level of the aqueduct to

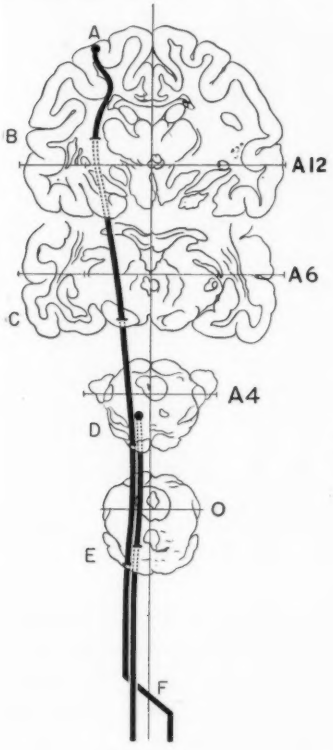

FIG. 1

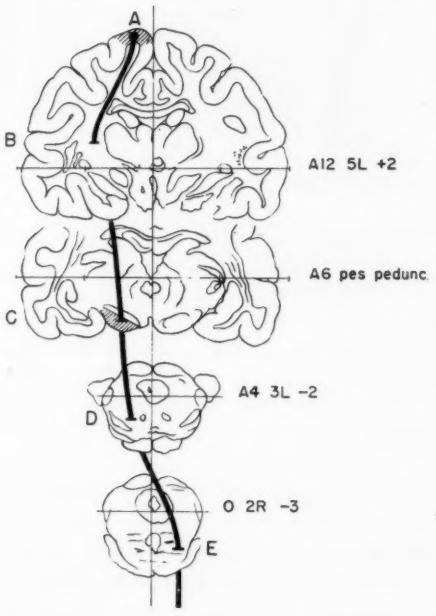

FIG. 1A

FIG. 1.—A diagrammatic representation of the regions giving inhibition of the knee-jerk and the approximate situation of lesions.

FIG. 1A.—A diagram of the first conception of a single decussating inhibitory pathway.

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the red nucleus. More ventrally, however, stimulation of the cerebral peduncles causes predominantly contralateral inhibition (fig. 2).

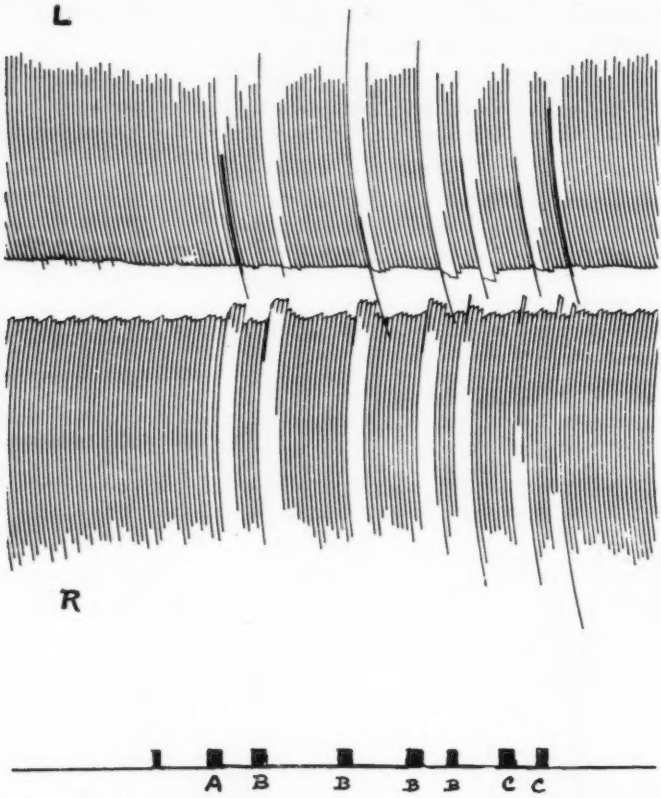

FIG. 2.—*Cat* 45. Stimulation (1·5 volts) at Ant. 4: R3. (A) at 0– ipsilateral inhibition. (B) at –1 to –4 bilateral inhibition. (C) at –5 and –6 contralateral inhibition.

Inhibition from any region may consist either of simple suppression of the reflex, more or less complete, or of suppression accompanied by movements of the affected leg. Motor activity involving the knee is identified with significant change in the base-line during stimulation and is considered to be predominantly extensor when in the same direction as the reflex, flexor when in the opposite direction.

With the electrode remaining at a given point, a small change in stimulus may introduce or eliminate the movement with negligible change in the degree of reflex inhibition. Thus, on stimulating in the internal capsule (with 2 volt 60 cycle A.C.) at the Horsley-Clarke co-ordinates

anterior 12, left 5, minus 2, the knee-jerk is inhibited with strong flexion at the knee. When the stimulus is diminished by a half volt, there is now complete inhibition but no recorded movement of the leg, as shown in fig. 3. Possibly an inhibitory effect on the stretch reflex precedes move-

FIG. 3

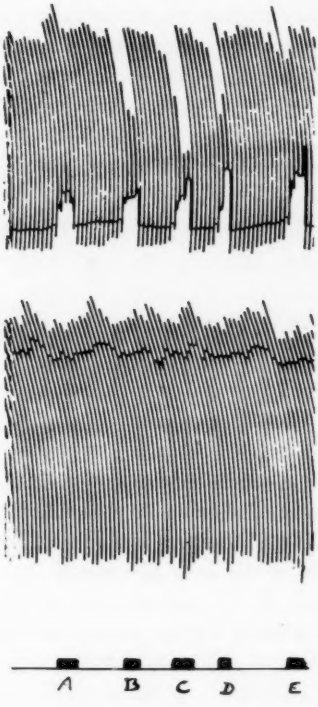

FIG. 4

FIG. 3.—*Cat* 44. Stimulation at Ant. 12; L5; −2. (A) 2 volts—extension. (B) 1·5 volts—inhibition.

FIG. 4.—*Cat* 25. Stimulation (2 volts) at Ant. 12: R5: +1 to +5. Inhibition with flexion maintained throughout stimulation. "Holding reaction."

ment at an initially lower level of stimulus. Sometimes movements are abrupt and violent; on other occasions they are delayed, slow, progressive and maintained, and of variable amplitude. The first is suggestive of a "phasic" type of movement, the second of a "plastic" type, but neither shows definite specificity of localization (fig. 4).

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Movement is not always associated with reflex inhibition; sometimes the reflex response is only reduced in amplitude; more rarely it is facilitated. Movement almost always does occur, however, at the point of maximum inhibition; and the two vary together throughout the decussation previously described.

(3) *Effects of Lesions*

After the foregoing experiments had provided an outline of the inhibitory regions from the cortex through the mid-brain, a further series was performed employing acute and chronic lesions. On five occasions, after recording inhibition from the region of the internal capsule and from the prerubral field, acute sensorimotor decortication was carried out. Neither unilateral nor bilateral acute decortication interfered with inhibition.

In order to show that descending pathways only were acting upon the lower centres and that ascending influences were not at work on the cortex (possibly through thalamic relays), three acute experiments were performed in which the whole brain was sectioned in the coronal plane at the level of the head of the caudate nucleus. Results of subsequent stimulation were unaltered.

Both from the low threshold of stimulation and from the lack of effect of cortical destruction it appeared that descending fibres only were involved and not groups of nerve cells. Therefore the pathway was further investigated by placing lesions along its descending course; a superior point of inhibition being located and the effects of stimulation observed before and after making a lesion at a lower level. From cortex to the caudal region of the internal capsule there is a continuous pathway of inhibition; lesions by electrocoagulation along its course prevent inhibition from higher levels. High section of the pes pedunculi, in acute experiments in seven cats, abolished inhibition and movement from stimulation anterior to the section. In the tegmentum, however, inhibition was normal.

Electrocoagulation lesions were next made in areas of ipsilateral inhibition in the pre-rubral field. Since inhibition from the internal capsule was invariably contralateral, it was thought that such a lesion might interfere with inhibition from the opposite internal capsule. These lesions were not effective, however, nor did bilateral lesions in inhibitory regions of the prerubral fields prevent subsequent inhibition from either internal capsule.

Chronic unilateral sensorimotor decortication, under aseptic conditions, was performed on two cats and intervals of four months and four weeks allowed for degeneration of corticofugal fibres. In both cases it was im-

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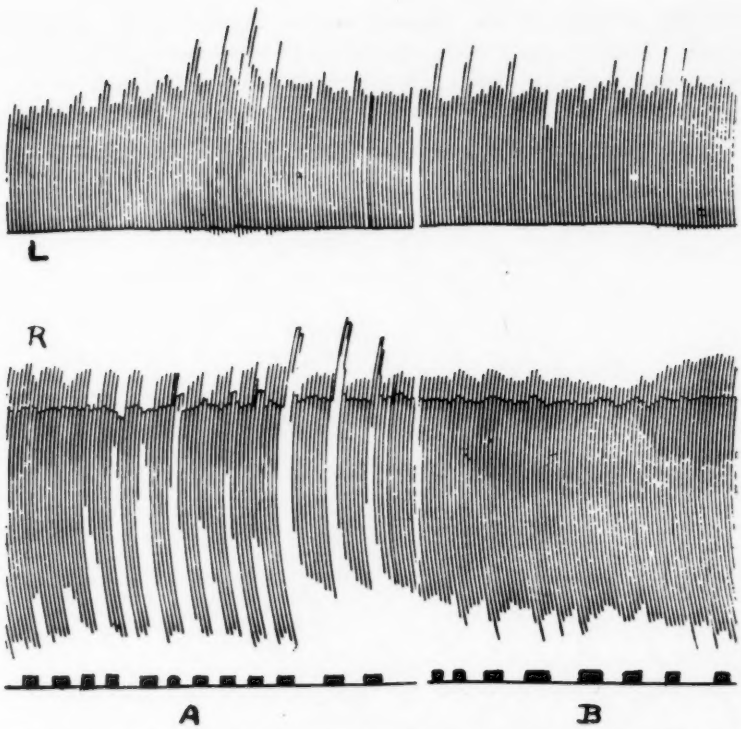

FIG. 5.—*Cat* 38. Chronic right sensori-motor decorticate preparation. Stimulation (2 volts) at Ant. 10: Lat. 5: +2 to −3. (A) Stimulation of left side gives normal contralateral inhibition with movement at points of maximum response. (B) Stimulation on right side. No response except slight bilateral facilitation.

possible on the operated side to obtain inhibition by stimulation anywhere from the zone of decortication down to the tegmentum. Not only was inhibition abolished, but also associated movement (fig. 5). But from the tegmentum and more caudal regions, inhibition was obtained as on the normal side, the inhibition being contralateral, bilateral or ipsilateral according to the level of stimulation. Chronic bilateral decortication, in harmony with the above, did not affect inhibition from the mid-brain and pontine tegmentum.

These observations indicate the existence of two independent systems of inhibition operating in this area, as will be discussed.

(4) *Facilitation*

In all acute experiments facilitation of the knee-jerk has been readily produced by stimulation of whatever brain-stem region was studied, but

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interesting changes of the bilateral picture appear as the electrode descends. There is also a fairly constant shift between excitation and inhibition with electrode depth. Thus frequently on stimulation at more superior points, say five millimetres above the Horsley-Clarke plane at a

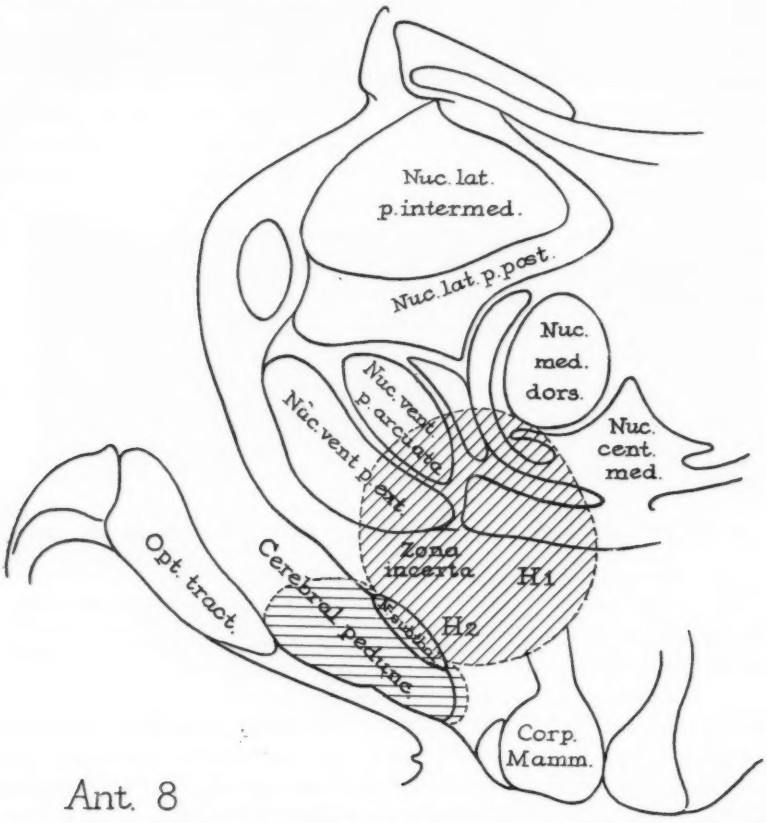

FIG. 6.—The shaded area represents the region producing inhibition of the knee-jerk at 8 mm. anterior to the Horsley-Clarke zero.

suitable antero-posterior level, bilateral facilitation is first encountered. As the electrode descends, millimetre by millimetre, facilitation becomes unilateral; then this shifts to unilateral inhibition and finally to bilateral inhibition. Similarly, on emerging on the distal side of a region of inhibition a zone of progressive facilitation may appear.

As previously described, chronic hemi-decorticate preparations fail to show inhibition in regions on the operated side which are strongly in-

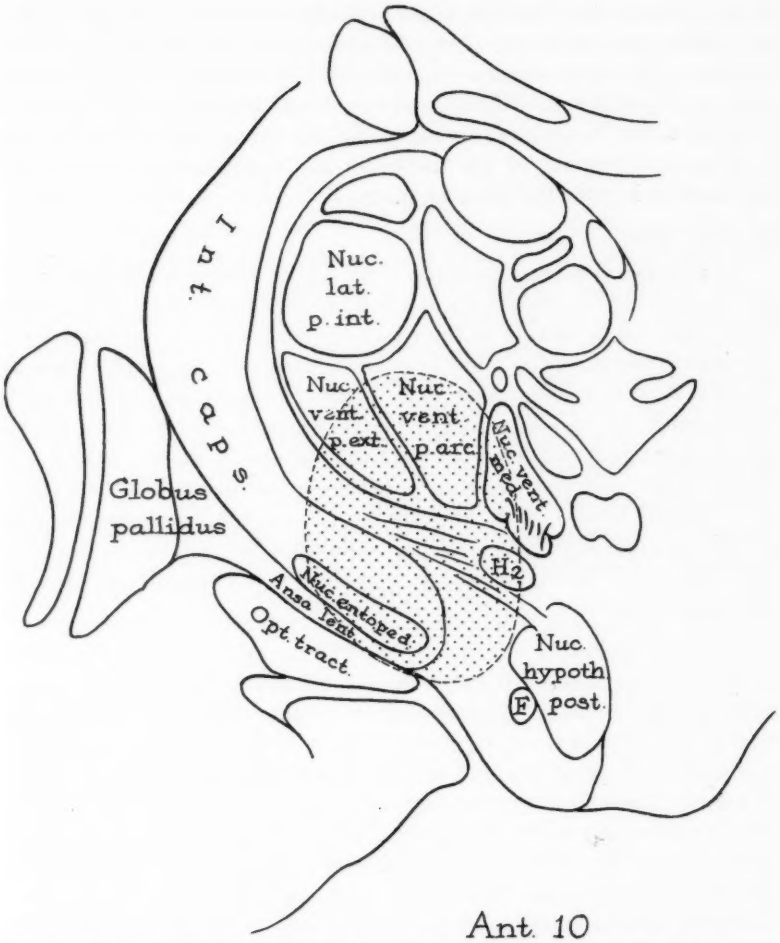

FIG. 7.—The shaded area represents the region producing inhibition of the knee-jerk at 10 mm. anterior to the Horsley-Clarke zero.

hibitory on the normal side. Invariably, facilitation appears on the abnormal side in those areas which are usually inhibitory.

Inhibition was not observed with oscillographic recording, in the monosynaptic response, with the animal under local anæsthesia and immobilized with d-turbocurarine, even though facilitation was easily obtained over a wide area of the brain-stem. The reason for the interference of curare with the usual inhibitory effects is not clear and requires further investigation.

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In all circumstances, however, when inhibition is lost for whatever reason, facilitation appears at the points of stimulation that normally give inhibition. Moreover, regions of inhibition are regularly surrounded by regions of facilitation. Thus it appears, from the diffuse distribution of facilitation and its appearance after loss of inhibition, that facilitation may be a general property of the mid-brain and upper brain-stem, possibly mediated by hypothalamic mechanisms.

(5) *Other Movements*

In addition to movement of the lower leg, we have also observed movements involving the whole body, one side of the body, or groups of muscles. These give rise to flexion of the trunk, suggestive of torsion movements previously described as the "tegmental reaction" (Ingram, Ransom, Hannet, Zeiss, and Terwilliger, 1932; Ectors, Brookens, and Gerard, 1938). Occasionally we have seen tremor of the face and anterior limbs similar to the rhythmic myoclonus of tegmental lesions of man. Jenkner and Ward (1953) produced this type of tremor experimentally in the cat at more caudal levels. Such movements are not always accompanied by inhibition of the knee-jerk. Pupillary dilation, which is frequently seen on stimulation in this region, is usually ipsilateral but sometimes occurs on the opposite side.

Discussion

In the early stages of the investigation the consistently outlined core of inhibitory tissue was thought to represent a single system (fig. 1A). The contralateral inhibition from the internal capsule being succeeded by bilateral and ipsilateral inhibition at lower levels was explained in terms of dissociation of inhibitory cortico-fugal fibres to mid-brain nuclei. The inhibitory effect of the rubrospinal tract on spinal activity was described by Rademaker (1926) and the decussation of this tract could be held responsible for the change in laterality. Subsequent experiments, however, involving acute electrocoagulation lesions, suggested the existence of a separate inhibitory system arising in the pre-rubral region. This interpretation was confirmed by the results of stimulation in the unilateral and bilateral sensorimotor decorticate preparations (fig. 1).

The inhibitory system, here described, can be considered in two parts in relation to the laterality of the inhibitory effect on the knee-jerks. The first, giving contralateral inhibition, consists of cortico-fugal fibres traversing the medial portion of the internal capsule and encroaching upon the external part of the caudate nucleus and the infero-lateral portion of the thalamus. As regards laterality this part of the system is then limited caudally by the appearance of the decussation, previously des-

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cribed, which commences in the pre-rubral field at 4 mm. anterior to the Horsley-Clarke zero, varying a millimetre or so from animal to animal in terms of Horsley-Clarke co-ordinates. At this point the inhibitory tract has taken up a more median situation and is lying 3 mm. from the mid-line. From here caudally inhibition is ipsilateral, after a short region giving bilateral effects.

The independence of the two parts of the inhibitory system, under the conditions of the experiments, is suggested by the finding that electro-coagulation lesions in the internal capsule, or section of the pes pedunculi, abolish inhibition from points of the "contralateral" part of the system anterior to these lesions but not from the lower "ipsilateral" part; whereas similar lesions in the lower part of the system leave inhibition from the cortex and internal capsule quite unaffected. This view was further strengthened by the experiments on the chronic decorticate preparations in which degeneration of cortico-fugal fibres was confirmed both by unresponsiveness to stimulation and by histological appearances. Movements and inhibition did not now occur on stimulation in the anterior part of the system, but they were quite unaltered from and posterior to the pre-rubral field. In the unilateral decorticates, the unoperated side remained normal and gave the usual contralateral inhibition.

It appears, therefore, that there is a second system of fibres concerned with inhibition arising in the mid-brain in proximity with the cranial end of the reticular formation, the fields H_1 and H_2 of Forel and the zona incerta. Inhibition here is predominantly ipsilateral, but is sometimes bilateral.

Throughout these experiments the association of inhibition and motor activity resulting from stimulation of a single point has been frequent. In a large proportion of instances the maximum point of inhibition, or the point where this can be obtained with minimal stimulus, also gives movement of the limb. The extensors and flexors are involved in varying degrees and marked tremor frequently accompanies strong contractions. These findings agree with the views recently expressed by Peacock (1954) on the effects of subcortical stimulation on cortically induced movements. In the mid-brain, in the region surrounding the red nucleus, movements corresponding in laterality with inhibition are a striking feature and are unchanged by cortical ablation and pyramidal degeneration. With stronger stimulation (5 volts at 60 cycles A.C.) in this region "the tegmental reaction" occurs, comprising patterns of movement involving the whole body musculature, respiratory changes, and frequently micturition. Weaker stimulation (1 volt at 60 cycles A.C.) gives more discrete movements and simultaneous inhibition of the knee-jerk. Possibly spread of current

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accounts for the total "tegmental reaction" resulting from stimulation of a single point in this region. With lower voltage stimulation there is partial elicitation of the reaction, presumably from effects on smaller groups of fibres; but throughout the motor and inhibitory effects are concurrent.

For reasons previously suggested it appears that inhibition in these experiments has resulted from stimulation of nerve fibres rather than cells. The final inhibitory phenomenon would then seem to occur at the spinal level. However, the connexion between the region of origin of the second system and the globus pallidus, by the ansa lenticularis, suggests an association of the second system with the efferent pathways of the basal ganglia. The hypertonia and tremor of Parkinsonism are to some extent mimicked in these animals during stimulation of pallido-fugal fibres. Recent surgical treatment of Parkinsonism has been directed by Meyers (1954) to the section of pallido-fugal fibres where these are concentrated in the ansa lenticularis. One of us has seen striking amelioration of rigidity and tremor following such surgical intervention by Guiot (1953).

Summary

(1) Central inhibition of the bilaterally evoked knee-jerk has been investigated in experiments on fifty cats.

(2) The region studied extends from the cortex to the pontine tegmentum.

(3) The almost constant association of movement with inhibition suggests that the latter is a motor effect.

(4) Two independent systems of nerve fibres mediating inhibition are described. The first is cortico-fugal, traversing the medial part of the internal capsule and involving the external part of the caudate nucleus and the infero-lateral portion of the thalamus. The second arises in the tegmentum in the region of the upper reticular formation and the efferent pathways of the basal ganglia.

We wish to express our indebtedness to Dr. R. W. Gerard for his encouragement and guidance in the work upon which this manuscript is based.

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NOTICES OF RECENT PUBLICATIONS

THE CEREBELLUM AND ITS DEGENERATIONS

Aspects of Cerebellar Anatomy. Edited by J. JANSEN and A. BRODAL. 1954. Pp. 423, 92 figs. Oslo: Johan Grundt Tanum Forlag. Price £3 15s.

Professor K. E. Schreiner, the Director of the Anatomical Institute of Oslo University from 1908 to 1945, reached his eightieth birthday in 1954. In honour of this occasion his colleagues and old pupils have taken the opportunity of collecting together in an impressive volume the results of their systematic investigations of the cerebellum. This is particularly appropriate, for over the last several years the difficult problem of cerebellar anatomy has been attacked with great persistence by a team of workers at Oslo University, and with considerable success. Professor Jansen is concerned in the first section of the book with the more strictly morphological studies, Professor Brodal and Dr. Walberg record and summarize the results of their experimental investigations of fibre connexions, and Dr. Harkmark gives an account of his ingenious experiments on the migration of groups of developing neuroblasts from the rhombic lip in the chick embryo. This last work is of unusual importance, for it has demonstrated for the first time that the migration is a true migration, that is, an actual movement of cells and not a relative displacement. Dr. Harkmark postulates an active amœboid motility of the individual neuroblasts to explain the migration, and he is frankly sceptical of a number of alternative theories which have held the field for many years, such as that of neurobiotaxis or the theory of fibrillogenic stimulation. As with so many hypothetical explanations of morphogenesis, the more naïve postulates of "Entwicklungsmechanik" appear to be becoming less and less satisfying in their application to the development of the central nervous system.

The main part of this volume on cerebellar anatomy is not easy to read, but it provides a useful work of reference to much that is now known on this complicated subject. Particularly valuable is the lengthy chapter on the structural organization of the cerebellum in which an attempt is made to interpret the results of functional studies in terms of anatomical connexions and localizations. Professor Schreiner may well be proud of this product of the Anatomical Institute which grew up and blossomed under the inspiration of his vigorous personality.

W. E. le G. CLARK.

The Spino-Cerebellar Degenerations. By J. G. GREENFIELD. 1954. Pp. 112. Oxford: Blackwell Scientific Publications. Price 17s. 6d.

It was surprisingly late in the history of neurology that the disturbances of function which result from disease of the cerebellum and its connexions were recognized and clearly differentiated; for instance, in members of two of the four families on which Pierre Marie based his description of hereditary cerebellar ataxia no essential changes were found in it. Later the symptoms that result from its disease, either alone or in combination with that of closely related structures, have been minutely described but few satisfactory attempts have been made to classify or arrange them in clearly cut or pathological groups.

The chief service of this small book is that it provides a critical analysis of the disturbances of function which characterize diseases of the cerebellum and of its

associated systems, and that it presents a scheme of classification based on the anatomical changes found in different forms of familial or hereditary ataxia. These, the author suggests, can be arranged in three main groups; one in which the spino-cerebellar afferent systems are mainly or exclusively involved, a second in which lesions occur in both the spinal cord and the cerebellum, and a third where the latter only or its more intimate connexions are affected. An analysis of the clinical symptoms as well as of the anatomical changes which characterize each type and their variations from family to family is a prominent feature of this monograph which will serve to clarify a complicated group of hereditary or familial diseases related to one another by signs of involvement of the cerebellum or of its afferent connexions. A very complete bibliography adds to its value.

GORDON HOLMES

THE PYRAMIDAL TRACT

The Pyramidal Tract: Its Status in Medicine. By A. M. Lassek. 1954. Pp. 166. Blackwell Scientific Publications Ltd., Oxford. Price 34s.

In the past few years Professor Lassek has laid us under an obligation by his remarkable studies of the constitution of the pyramidal tract, and by his demonstration that its fibres so far outnumber the giant cells of Betz that these can no longer be regarded as the sole, or even the major, source of the tract.

Thus, after many years, we have one more indication of the correctness of the dictum of Bevan Lewis in 1881 that the giant cells of Betz did not constitute a specific morphological category but were merely the largest representatives of a general formation of cells of wider distribution than Betz affirmed. Supported, also, is the view expressed by Barker (1899) that the pyramidal tract arose over a wider expanse of the cortex than was then, and is still, commonly supposed. Indeed, the term "giant cell of Betz" has never deserved the status of a term of scientific precision, for so long and so carelessly assigned to it.

It is perhaps disappointing that the author of this brief monograph has not given more consideration to his own personal contribution, for here at least he is on his own ground and can speak with authority. Interesting is the wide range of fibre calibres in the tract, small fibres predominating and so suggesting that the pyramidal is not a rapid conducting pathway. Elsewhere, with a disconnectedness shown so often throughout the monograph, the author cites without comment Foerster's view that the pyramidal is a "fast-train" pathway.

In setting out to summarize in so brief a compass the physiological and the clinical literature on the pyramidal system, the author has undertaken the impossible, and it is clear that the vast literature from both sources has defeated him in selection and in assessment. One of the reasons for the defeat in integrating and critically evaluating the sum of evidence is his unawareness of the besetting weakness of so much of this: namely, the common failure of writers to distinguish between the symptoms of lesions (experimentally produced or the result of disease) and the normal functions of the central nervous system. The necessity of making this distinction, so clearly expounded by von Monakow, so evident in the writings of Hughlings Jackson, and so often reiterated since their time, has never made an adequate impression upon workers in the neurological disciplines. To use a kitchen metaphor, there are almost too many pouring their fragments of information into the stockpot, but too few able to produce, or to see the necessity of producing, the clear soup of logical inference and well-based hypothesis. Professor Lassek here throws his fragments into this particular stockpot, some are edible, some are not, but no clear brew issues from his pages.

It is because the author ignores this problem of intellectual method that we

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encounter so many of the familiar and conflicting accounts of cerebral motor activities. Thus, in a chapter upon the results of the electrical stimulation of cortical points he reports without elucidatory comment that "skilled movements are never elicited from cortical stimulation, only those of simple flexion and extension of one or more joints. Motor behaviour is never more complicated than that the newborn infant is able to perform." The quotation is from Penfield and Rasmussen's monograph on the cortex, and surely the reader should be told that a mode of activation of the cerebral surface so grossly unphysiological—so inadequate in the Sherringtonian sense—cannot be expected to evoke anything resembling the normal activities of the intact cerebral cortex in the intact organism, that the absence of skilled movements in these circumstances cannot allow us to assume that these are elsewhere organized than in the cortex, and that the isolated responses to electrical stimulation do not resemble the normal activities of the newborn infant, yet it is the repetition of these unjustified inferences, these examples of the *non sequitur*, from paper to paper and from monograph to monograph that is the major factor in what Trotter so aptly called the "astonishing viability of the false."

In his selection of clinical sources the author is upon equally unfamiliar ground. Seventy years after Wernicke's postulation of the "Prädilektionstypus" of paralysis in upper motor neurone lesions, after Jackson's demonstration, so fully exemplified later by Beevor, that movements and not muscles as such are paralysed in these circumstances, it is surely not acceptable that we should be told that the result of such a lesion in hemiplegia is simply a paralysis of muscles [*sic*] of the distal parts of the limbs; no bilaterally innervated muscles being paralysed. This is as misleading as it is inadequate.

In a widely extended review of clinical literature of very variable quality, Lassek finds that there is no precise correlation between pyramidal tract degeneration and the presence of the extensor (Babinski) plantar response, and he expresses doubt as to the existence of any constant correlation between the appearance of the sign and the loss of function in the tract. The transient appearance of the sign in various toxic states and after epileptic convulsions seems to him corroborative evidence of the tenuity of any link between the sign and the system. He concludes that the mechanism of the Babinski is unknown and that it is of a sensitive and capricious nature.

This is not really an informative conclusion, nor does it do justice to the evidence as to what is believed of the nature of the response, and of its association with disturbances of function in the upper motor neurone. It is true that pyramidal tract degeneration in both cerebal and spinal cord lesions is often much less marked than might have been expected from the clinical picture, but the microscope has no longer the final word as evidence of disturbed function.

F. M. R. WALSHE.

STEREOTAXIS IN MAN AND CAT

Monographs in Biology and Medicine. Stereoencephalotomy. (Thalamotomy and Related Procedures.) Part 1. Methods and Stereotaxic Atlas of the Human Brain. By E. A. Spiegel and H. T. Wycis. 1954. Pp. 176, 79 figs., 31 tables. Grune and Stratton, New York. Price £3.

This monograph opens with a very detailed description of the design and construction of the authors, three stereotaxic machines: next follow full details of orientation of intracranial structures by straight radiography or air encephalography, should pineal or habenular calcification be not present. The mathematical calcula-

tions required to place the lesion accurately are explained clearly and concisely being followed by an account of the surgical operative technique. A large section is then given to a stereotaxic atlas, both macroscopic and microscopic, which runs into nearly fifty full page plates and is preceded by a description of the mode of fixation in situ of the thirty brains studied to compile the atlas. The authors go on to a valuable chapter on the variability in size and position of various anatomical structures.

In a series of twenty cases a pantopaque droplet was injected at the site of the electrosurgical lesion so that subsequent radiograms could be taken to compare the actual site of the lesion with that intended pre-operatively. In twelve of the twenty cases the lesion was within a millimetre of that which had been designed, showing that a high degree of accuracy can be obtained by the method. In only one case was the actual lesion as far as 3·5 mm. away from the chosen site.

Finally four post-mortem studies are described showing the lesions produced by the method in patients succumbing some weeks or months later.

This monograph is a new and fascinating study in the field of neurological surgery, which has been compiled with great care and attention to detail and reflects much credit upon the authors. It is beautifully produced and illustrated by many diagrams and photographs, the latter being of a very high order of excellence. It is a production which must be in the hands of all who are pursuing stereotaxic methods.

W. McKISSOCK.

A Stereotaxic Atlas of the Diencephalon of the Cat. By H. H. JASPER and C. AJMONE-MARSAN. National Research Council of Canada, Ottawa. 1954. Pp. 70, 26 illus., 33 figs. Price 10 dollars.

The authors of this atlas have used the stereotaxic instrument for some fifteen years, and their contribution is based not only on this personal experience but on that of a number of other investigators. The publication consists essentially of a series of coronal sections (photomicrographs of Nissl and Weil sections and drawings) through the diencephalon of the cat. The illustrations are reproduced ten times natural size so that measurements can be made directly with a centimetre rule and expressed in millimetres. The material presented, and the hints on technique given, will be invaluable to anyone engaged in work involving precisely localized lesions. The book will also be helpful to those interested in the anatomy of the cat's brain and is an object lesson for those who doubt the ability of experimental neurologists to place lesions just where they are desired. Printing and reproductions are excellent, but the binding provided hardly does justice to the authors' and printer's work.

J. D. BOYD.

ELECTROENCEPHALOGRAPHY AND EPILEPSY

Supplement No. 4 of Electroencephalography and Clinical Neurophysiology. Pp. 260. Montreal.

In this volume are recorded the symposia of the third International Congress of Electroencephalography held in Cambridge, Mass., in August 1953. As each of six symposia was opened by two or three authorities, the book gives a wide representation of contemporary views in this subject. Any single reader will find parts unintelligible to him, for the contributors included physicists, physiologists and clinicians, and electronic technologists will probably find it much more easy going than clinicians. The first two symposia dealing with techniques and the physiological basis of the electroencephalogram consist of applied physics, but the remain-

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ing four, on activation of the electroencephalogram; interrelationships between cortex and subcortical structures; the electroencephalogram in infancy and childhood; and seizure discharges are immediately applicable to current clinical problems.

The study of the electrical concomitants of *petit mal* led to exploration of the rhythmic electrical activity of the basal grey matter, and then naturally to enquiry into the time relationships between discharges or rhythms in cortex and subcortex. At the same time observation of the remarkable effects of lesions of the mesencephalon on behaviour and consciousness, led to study of the associated electrical changes, and it became apparent that mesencephalon, thalamus, the fimbrial region and whole cortex were involved. Links were seen with the old histological work on uncal lesions in epileptic patients, and the ubiquity of the spike and wave discharge in *petit mal* was related to the mesencephalic-thalamic changes. It was fitting that Professor Bremer opened that discussion, that the anatomy was covered by Droogleever Fortuyn and the physiology by Magoun, while Jasper dealt with the application to human epilepsy.

This volume gives an idea—often confused—of this major trend in neurophysiology, it shows how near the beginning the research we are, and it emphasizes that the future depends on teams and not individuals.

The Epilepsies—Electro-Clinical Correlations. By HENRI GASTAUT. Translated by Mary A. B. Brazier. 1954. Pp. 149. Oxford: Blackwell. Price 34s.

The time was ripe for a statement on how electro-physiological methods have altered our attitude to the epilepsies. In ordinary clinical practice an electroencephalogram has become just another test, usually disappointing but sometimes startling. Classifications of the epilepsies based on electro-encephalographic findings alone were unsatisfactory to the clinician, but from the beginning it was amazing how divisions based on clinical evidences were confirmed by the electrophysiologist. There were, however, many anomalies, such as the epileptic attack without any overt electro-encephalographic accompaniment, but activation techniques and direct recording from the cortex and from subcortical structures are now showing changes invisible in the ordinary electro-encephalogram. Today very detailed study of special cases with the full co-operation of a large team of surgeons and physiologists is proving most profitable. It is in this field, and especially in the use of activation techniques, that Professor Gastaut's interests lie.

The present small book summarizes the results of his work over the past ten years, and relates it to that of other centres, particularly that in Montreal. It is probably the most lucid and succinct monograph on epilepsy since the last of the great clinical descriptions. It has the approach of a physician, though much of the evidence in it is electronic, and it has a holistic character unusual in this field today. In a changing and controversial subject, Professor Gastaut's attitudes and generalizations are most welcome while the value of the material presented has been enhanced by a free and idiomatic translation. The book is warmly recommended to all interested in abnormal brain function.

DENIS WILLIAMS.

CLINICAL PSYCHIATRY

Clinical Psychiatry. By W. MAYER-GROSS, E. SLATER and M. ROTH. 1954. Pp. 652, 21 illus. Cassell, London. Price 50s.

The authors of this impressive textbook of psychiatry leave the reader in no doubt where they stand in the major controversies that beset the subject. They

do not accept the psychoanalytical theory or the psychoanalytical method of inquiry, they are convinced that the foundations of psychiatry must be laid on the ground of the natural sciences. they believe that the pathological basis of schizophrenia is organic, and they are sceptical about preventive measures at present applied, or proposed for application, to children. Their outspokenness on these and other disputed issues is welcome. No one who wants to see psychiatry through Freudian or Jungian spectacles will be deceived into thinking that this book will give him what he likes, and those who wish to become better acquainted with a consistent, traditional viewpoint, expressed lucidly and often with felicity, will find it readily here.

Critical and sometimes dogmatic, impatient of subtleties and fortified with ample clinical detail and concise argument, the presentation has the weight and in some respects the impetus and self-assurance which used to characterize German psychiatry. Indeed the solid contributions of German psychiatry, especially during the first two decades of this century, are rightly drawn on more here than has been customary, and in spirit and purpose the book seems closer to Bumke's Lehrbuch than to any of the more familiar texts.

The authors have deliberately omitted any general section because they would have felt obliged to discuss in it philosophical problems, and they think psychiatrists have devoted too much time and thought to these abstract issues instead of confining themselves to "their main task, the attempt at a comprehension of observable facts." Philosophical questions, however, occupy comparatively little of the space usually taken by the general section of a psychiatric textbook, and it would have given the exposition a more explicit framework if, leaving philosophy aside or treating it with exemplary concision, they had provided a broad general survey, especially of the contributions of modern psychology to psychiatry, and an indication of the assumptions or theoretical systems on which their accounts of disturbance of thinking, perceiving and acting are based. The psychopathology of thought-disorder, for example, can hardly be examined and understood unless its experimental and conceptual origins in psychology are recognized. The influence of Karl Jaspers is to be discerned in the expositions of psychopathology, which are given in the context of special clinical problems; and the authors do not much concern themselves with the dynamic aspects of human behaviour. They are in general tepid in their appreciation of what the social sciences can now add to psychiatric knowledge, and they assert, with manifest bias, that "sociological work is actually of more importance to general medicine than to psychiatry."

Among the striking features of the book are the comprehensive, well-documented chapter on ageing and the mental diseases of the aged; the wide coverage of administrative and legal aspects; the omission of illustrative case-records; and the inclusion of psychopathic personality and neurotic reactions under the same rubric.

Its outstanding merit lies in its straightforward, detailed, readable account of syndromes, and its sincere and discriminating effort to incorporate the valuable findings of clinical, biochemical, genetic and pathological research into mental disorder. With these and other virtues go a slightly querulous, pragmatical tone here and there, and a robust attitude towards alleged error which reminds one at times of Dr. Johnson's way of refuting Bishop Berkeley. To Adolf Meyer's teaching and achievements the authors do much less than justice.

This textbook will have a deservedly wide currency, even among those who do not agree with the authors' avowed standpoint but recognize their experience and erudition.

A. J. LEWIS.

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NOTICE

IV SYMPOSIUM NEURORADIOLOGICUM

The meeting will be held in London from September 13-17, 1955. Registration will take place on September 12 at the University of London, Malet Street, W.C.1, where the scientific meetings will be held. Radiologists, neurologists and neurosurgeons particularly are welcome.

Subjects for discussion include (i) cerebrovascular disease, (ii) the localization of intracranial tumours by means of isotopes, (iii) applications of stereotaxometry, (iv) new techniques and (v) various proferred papers on a variety of neuroradiological subjects. Scientific and technical exhibitions are being arranged.

It is hoped to arrange a joint half-day session with the 2nd International Congress of Neuropathology which is being held simultaneously in London.

A full social programme has been arranged including visits to places of interest for wives and families of members.

Those who cannot spare the time are invited to become day members at a much reduced subscription rate.

Application forms and further information may be obtained from Dr. R. D. Hoare, Secretary, Symposium Neuroradiologicum, The National Hospital for Nervous Diseases, Queen Square, London, W.C.1.

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